EXHIBIT 5

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE:

SEROQUEL PRODUCTS LIABILTY LITIGATION

CASE NO. 6:06-md-01769-ACC-DAB

MDL DOCKET NO. 1769

April 24, 2008

CONFIDENTIAL Videotaped Oral Deposition of KEVIN GEOFFREY BIRKETT, held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, Philadelphia, Pennsylvania beginning at approximately 9:00 a.m., before Ann V. Kaufmann, a Registered Professional Reporter, Certified Realtime Reporter, Approved Reporter of the U.S. District Court, and a Notary Public.

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
Philadelphia, Pennsylvania 19103
877.370.3377

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A. It was more based on market experience than testing.
Q. Okay. And then as part of marketing do you also get involved in delivering the message?
A. We in the global function would deliver the global strategy, which would lay out the key claims that we felt were most important to the brand. We'd also lay out the long-term plan for the brand. The local messages in the U.S., China, Japan, U.K. would be done by the local operating company.
Q. Okay. So you guys were involved with the overall strategy for developing the message, testing the message, and then you would provide it to the local companies in the U.S. or wherever to deliver the message; right?
A. We were really testing the product, suggesting the optimal message. And then how the product was promoted locally varied upon local market circumstances and the label in

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that country.
Q. Okay. But there were core messages that the company developed; right?
A. Yes. But whether they could be used in absolute and every marketing company was very rare, for various different reasons.
Q. Okay. But there was a core message group, wasn't there?
A. There wasn't a group called the core message group.
Q. No, I'm sorry, I wasn't making myself clear. There were core messages that the company developed; right?
A. Yes.
Q. For Seroquel?
A. Yes.
Q. Okay. And then there were core -- there was actually a core detailing set of slides that was available as well; correct?
A. I don't think that's a good

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terminology and it's not what I'm familiar with. There was a core set of messages that we were recommending the marketing companies would use if the clinical trials delivered the data to support them. There was no global detail aid. Detail aids are very prescriptified and used in one country. I think it's not valid to have a global detail aid.
(Below-described document marked Birkett Exhibit 2.)
BY MR. BLIZZARD:
Q. I'm going to show you what I'm going to mark as Exhibit No. 2. And I will hand one to your counsel.
MR. AUSTIN: Thank you.
Q. Could you tell me what this is?
A. This is an item called a sales story flow. It's not a detail aid. This is a means to say to the marketing companies that as the clinical results of our product unroll, we would

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like this to form the basis of our arguments that we use when promoting Seroquel in different markets around the world.
Q. Okay. If you turn over to the Page 3, which is the first page that contains details about the -- what this document is, do you see what it says there?
A. Yeah, a core detail flow.
Q. Okay. So this is to be used with -- in detailing, isn't it?
A. No. There's a difference between a detail flow and a detail aid. This is to give people a guide. A detail aid is a document that's used in practice.
This document was never printed and never used in a marketing company. This was to guide people in marketing companies. The detail aid would be a glossy printed item that would be used to promote to doctors.
Q. Okay. Now I see what

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distinction you are making. You are saying that this was the document that originated from your group that went out to all the marketing companies that proposed a flow of detailing when salespeople actually went into doctors' offices?

A. No. This was designed to give to the marketing people in the different markets to say to them that this could be a good detail flow to use if the data supports it, if your local label supports it. But the ultimate decision of what would be promoted country by country and in some instances would mirror this and in some instances would be completely different.

Q. Hold on a second. Who prepared this?

A. A global brand manager.

Q. And who was that?

A. Alison Wilke.

Q. And did she work for you?

A. She worked for somebody who

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worked for me, the global brand director.

Q. Okay. So she was under your direction; right?

A. Yes.

Q. And actually if you look at this document, doesn't this document say -- give proposed things to say to doctors to deliver messages to doctors about Seroquel based upon data that this Alison Wilke is saying is available and it supports these claims?

A. Yes; but every time this was reviewed by an individual marketing company, it would be reviewed by their clinical and regulatory team. And they would say this may or may not work in America, France, China, or Germany. They had to take global responsibility based on their local data.

Q. Okay. You are not trying to avoid responsibility for this, are you?

A. No, no. I think these

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documents are a very good guide, but they should never be used by a marketing company without it being rigorously approved by all of their local team.

Q. Okay. Well, did you guys look at this rigorously?

A. This was looked at rigorously by the commercial team and the clinical team.

Q. Okay. Within your group?

A. The clinical team wasn't in my group. That's a separate group.

Q. Okay. Did they provide support for your group?

A. Yes.

Q. Okay. So with the support of the clinical group, this was examined rigorously; correct?

A. Yes.

Q. And then sent out to the marketing companies throughout the world who were also supposed to look at it rigorously; correct?

A. Let me check, because the

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problem with this form is I don't even know if this ever went to the marketing companies. So from this, what you have shown me here, this may have been a draft document. It looks like it was. And so I don't even know that this went to the marketing companies.

Q. Do you know it didn't?

A. I don't know it did.

Q. Well, do you know it didn't?

A. No, I don't know it didn't.

Q. Okay. Well, let's look at some of the things that are said here. If you look at the first page, where it says "The following pages represent a core detail flow and backup data" --

MR. AUSTIN: I'm assuming you mean Page 1?

MR. BLIZZARD: No. I actually mean the third page, which is the page that has the substance of -- where the substance of the document begins.

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analysts.
Q. Well, you are correct about that, but it's not limited to pharmaceuticals, is it?
A. Certainly not. But it's limited to the financial analyst community; they are the people who generally are interested in Reuters.
Q. Yeah. Do you know what its reach is?
A. I don't know.
Q. Do you know what "reach" is?
A. I do.
Q. And what does it mean?
A. It means the number of people that you can reach through a specific medium.
Q. Okay. Is it an international or worldwide service?
A. Reuters is international.
Q. Okay. It says in the first paragraph: "I called our friend at Reuters - he was very personable but

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equally probing - more so than usual." So he was asking some tough questions?
A. Yes.
Q. Okay. It says: "I didn't give any hard facts but said the following after an intense battering of questions - I stuck to my 'script.'"
A. Yes.
Q. So you had a script for this interview?
A. No. But what we tended to do was that we had regular meetings with the people in our corporate headquarters at Stanhope Gate. We gave them the key points of note on any product because they like to be appraised of latest developments. I just used the script that we gave them so that I knew that I wasn't going to go anywhere that the company didn't want me to go.
Q. Okay. And that's generally what you did when you talked to reporters; correct?
A. Yes. The issue with

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talking to reporters, as I'm sure you are aware, they can be, as I point out here, extraordinarily probing and they can take some of the things that you tell them out of context. So I was trying to be extremely careful.
Q. Okay. Look over on the second page. It says: "He finished (sic) on why Zyprexa was doing so badly" -- do you see that paragraph?
A. Yes.
Q. -- "and asked if it was weight - I said weight - eps and a number of issues where we had superior offering." Do you see that?
A. Yeah. And that's absolutely correct.
Q. Well, did you -- you had an opportunity to tell him about the EPS findings that you had recently learned about with respect to your own product; right?
A. But the issue is we wouldn't be comparing apples with apples

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if I did that.
Q. Nonetheless, you had an opportunity within a month of finding out about these EPS findings to get the word out about what the findings were; right?
A. It would not have been appropriate. It would not have shown a good balance of data across the overall database for Seroquel to make that conclusion at that time. That's why the team were running extra studies.
So what I was saying here very clearly was in the treatment of schizophrenia and mania, which are the labeled indications for Zyprexa and Seroquel, because Zyprexa has much more EPS and much more severe weight gain, that's why we're winning and they're losing, which was factually correct.
Q. Well, I guess -- was telling them about Seroquel's EPS findings on the script?
A. I don't know how the script

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currently reads; but up until we decided to do another study from BOLDER, we always said that Seroquel in the treatment of schizophrenia and mania had a unique EPS tolerability profile, which it did, and I believe it still does.

Q. That was actually the cornerstone of the marketing strategy for Seroquel, wasn't it?

A. There was actually three points to the promotion.

Q. What were they besides superior on EPS?

A. Unsurpassed efficacy, superior EPS to all other agents and similar to placebo, and negligible prolactin and sexual side effects --

Q. Okay.

A. -- which were unique.

Q. And those three claims were the cornerstone of the Seroquel marketing strategy; correct?

A. Yes.

Q. Okay. Now I'm going to

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hand you what I'm going to mark as Exhibit No. 29 to your deposition.

A. Thank you.

(Below-described document marked Birkett Exhibit 29.)

BY MR. BLIZZARD:

Q. After you received these surprise -- is it fair to say that these findings on EPS in the BOLDER study came as a surprise to you?

A. I was surprised. I wasn't shocked. And we'd always postulated that when you indicate a product for a new series of disease targets, you'll have a different efficacy and side effect profile. So to have an EPS profile similar to placebo was an extraordinary thing. And we weren't arrogant enough to think that if we indicated Seroquel in all these different diseases, that would always remain.

Q. Right.

A. So surprise; not shocked.

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Q. Okay. And that's another reason why you don't want to promote for off-label use, correct, because the side effect profile might be different in a different population? Right?

A. That's why we never promoted off label.

Q. Okay. Because that could cause patient safety issues, couldn't it?

A. If doctors decide to use a product off label, it's outside the reach of the data sheet and our purview, and that's why we never promoted off label.

Q. Okay. And whether you are promoting it off label, educating people about it off label, or encouraging off-label use, you can run into some surprise side effect profiles if you have it used outside the label; right?

A. Any product if used by a clinician outside its label in a specific country could give results that

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are a surprise to the clinician and the company.

Q. Okay. Now, when you received these surprise findings about EPS coming out of BOLDER, did you take a look at some of the other studies that had previously been done to determine whether they were consistent or inconsistent?

A. No. But I remember that the head of our clinical team at the time asked for that analysis, which I applauded as a very good thing to do.

Q. Okay. And who was that?

A. Bob Holland.

Q. Okay. now, if you look at the last e-mail on the first page of this exhibit, do you see that this is written by a -- by Martin -- actually by Didier -- how do you pronounce that last name?

A. I think it's Didier Meulien. I'm sort of --

Q. French?

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have sworn under oath -- it's going to be on the record and the jury is going to see it -- that the marketing department was consulted on the core data sheet, and my only question is what was the consultations on the core data sheet involving Seroquel? What was the marketing department's role in that consultation?

MR. AUSTIN: Object to form.

A. To be aware of the discussions and the clinical and scientific rationale around why the data sheet may change.

Q. Why did you need to know that?

A. Because ultimately when the data sheet changed, we would have the responsibility to promote the product.

Q. And so, therefore, your promotion and what you may say or may not say could be affected by the core data sheet; right?

A. The core messages that we

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would try and deliver for any product of course had to be in line with the core data sheet; but the core data sheet was the ultimate document and it was a technically derived document.

Q. So if hyperglycemia and diabetes were added to the core data sheet, it could affect your role in marketing about what you could say and couldn't say about the product; correct?

A. Not necessarily. I think it's very important to just remind everybody that the key rationale and benefit for Seroquel in all my times in AstraZeneca was unsurpassed efficacy, excellent tolerability on EPS, and excellent tolerability on prolactin.

MR. ALLEN: We're going to take a break right now. But when we come back, I want to remind you of that "unsurpassed efficacy." We're going to pick that up after the break.

THE WITNESS: All right.

MR. ALLEN: All right.

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Thank you, sir.

THE WITNESS: Thank you.

THE VIDEOGRAPHER: It's 25 minutes after 10 o'clock. Going off the record.

(Recess.)

THE VIDEOGRAPHER: It's 39 minutes after 10 o'clock. It is Tape 2. We're back on the record.

BY MR. ALLEN:

Q. Ready to proceed?

A. Yes, thank you.

Q. "Unsurpassed efficacy," that's another one of your exaggerations, isn't it?

MR. AUSTIN: Object to form.

A. No, it's not an exaggeration. It was our way of explaining that Seroquel showed excellent efficacy versus older and newer agents.

Q. But that wasn't true, though, was it?

A. Seroquel at the correct

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dose shows excellent efficacy, and our belief is that in the correct target patients it is unsurpassed.

Q "Unsurpassed," what does "unsurpassed" mean? I think I know what it means but I want to make sure you and I are communicating.

A. It means in the correct patient treated for the correct indication at the correct dose Seroquel is highly effective and there's nothing more effective.

Q. Nothing more effective?

A. In the right indication at the right dose.

Q. And the right indication would be what?

A. It depends, because now for Seroquel we're lucky enough to have many indications.

Q. Oh, okay. Well, let me talk about -- let's just take schizophrenia first. Does dose have unsurpassed efficacy in schizophrenia?

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A. Seroquel in schizophrenia has a completely unique profile.
Q. Sir, I asked you does it have unsurpassed efficacy.
A. At the correct dose Seroquel is highly effective for the treatment of schizophrenia.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I didn't ask you that. You made the point to Mr. Blizzard yesterday and to me right before the break, and I told you I was going to come back to it, that Seroquel had unsurpassed efficacy. And I'm asking you under oath, does Seroquel have unsurpassed efficacy in the treatment of schizophrenia?
A. At the correct dose in the correct patients, yes, it does.
Q. And when did you have that opinion?
A. My opinion was formulated

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after speaking to all our scientists and after the research program and the regulatory program.
Q. So sometime in the '90s?
A. I first formed the view that Seroquel was an effective and safe product in the '90s, correct.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'm not going to let you change my question, sir. When did you form the opinion that Seroquel had unsurpassed efficacy? When was that?
MR. AUSTIN: Object to form.
A. I can't remember when our global product team decided that that was how we were going to characterize Seroquel's effectiveness. I cannot remember; I'm sorry.
Q. "How we're going to characterize." So, as you've already told us, you did use, "you" being your company, use the characterization of

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unsurpassed efficacy in your marketing efforts, did you not?
A. Yes, we did.
Q. Thank you, sir. Do you have anything else -- I'm sorry. Do you have anything else you want to say about that?
A. All of our marketing efforts were based on the labels in the individual countries where the product was marketed, and all of the claims we made were absolutely in line with the local core data sheets.
Q. But isn't it a fact the data didn't really look good concerning that issue? And, in fact, the data didn't look good at all and your product, Seroquel, did not even have unsurpassed efficacy over first-generation Haldol; isn't that right?
A. No. At the correct dose in the correct patients Seroquel is highly effective for the treatment of schizophrenia.

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MR. ALLEN: I got one, I got one here, but I need one without; okay?
Q. Sir, I'm trying to get a highlighter. This highlighter ended up with ink on the end so so when you highlight turns black, so I apologize. It will probably happen again.
Do you know that your company, AstraZeneca, did an analysis of the studies done on Seroquel in -- as of around March of 2000 and determined that in fact the data didn't look good and Seroquel didn't have as much efficacy as even Haldol? Did you know that?
A. I know you are looking at a report and you are asking me a question, and I don't remember a specific report that made the conclusion that you are referring to.
Q. Did you ever -- were you ever told by any individuals -- and I'm paraphrasing, but I'm paraphrasing pretty accurately -- concerning the claim of efficacy greater than Haldol in

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highlighting it for you.
A. Yes, I've got you.
Q. Those are Bates stamps. That's some lawyer term; I have never known what it meant. I guess Mr. Bates invented the stamping system. But that's called a Bates number; okay?
A. Thank you. I've been wondering what it was.
Q. And all I know is we call it that. I don't know anything else. But that's a Bates number.
A. Okay.
Q. I would like you to turn to Bates number page, last two digits, 89; okay? And it is under the heading "Proportion of responders." And, again, I'm not going to read that to you today. We will look at it later. But I want you then to turn the page --
A. I'm sorry. Do you want me to read this or not? I'm sorry.
Q. No, sir.
A. Okay.

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Q. I just wanted to orient you and the jury where we are. "Proportion of responders."
A. Okay.
Q. We turn the page to Page 90 and it is Table 1.
A. Yeah.
Q. Do you see that? And then in very plain English it says: "The following table is an attempt to simplify the claims that could be obtained from these results. A check is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or...last value carried forward." That's LVCF. "An X marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel." Do you see that?
A. I do, thank you.
Q. So a check is where Seroquel wins and an X is where the

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comparator wins. Do you see that?
A. I do.
Q. Comparators are listed under Table 1 and we have Placebo, Haloperidol. That's Haldol, is it not?
A. It is.
Q. Chlorpromazine, do you know what that is, ?Clozaril?
A. That's not Clozaril.
Q. What is that? Tell me what that is; I'm sorry.
A. It has a whole different series of names depending on which country it exists.
Q. Okay. What is chlorpromazine? Do you know what that is?
A. It has got so many different trade names that it's generally used by the generic.
Q. You are right. And I forgot. So that's an antipsychotic, is it not?
A. Yes. It's a 50-year-old

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antipsychotic.
Q. That's right. And you are right and I was mistaken. It is a first-generation antipsychotic; correct?
A. Yes, it was one of the first ones.
Q. Yes, sir. You are right. I apologize. We have Risperidone, which is Risperdal, and then other typicals. Do you see that?
A. I do.
Q. A check is where Seroquel wins and, guess what, Seroquel beat a placebo; right?
A. Yes.
Q. And an X is where the comparator wins. On Haldol we have three Xs, do we not?
A. Just, if you wouldn't mind, if I could just study the table.
Q. Yes, sir.
A. Yes, it says here that in this analysis haloperidol scores higher on BPRS, Factor V, and Hostility.

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Q. Yeah. Where did Seroquel score better?
A. It's hard to tell from this analysis, and I don't like the way it's presented, so --
MR. ALLEN: Sir, I object as nonresponsive.
BY MR. ALLEN:
Q. Quite frankly, it is not important whether you like it. Your company wrote this document. "A check is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with" a high dose and "be it using observed cases or...last value carried forward."
I'm asking you, in the comparator to Haldol, where did Seroquel win, according to Table 1?
A. From this table, from a document that's eight years old that I never saw that was never signed, I cannot see where Seroquel is seen as more effective than haloperidol.

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Q. And then chlorpromazine -- I think I'm pronouncing that right -- chlorpromazine, where did Seroquelwin?
A. It looks like -- in fact, I can't tell from this analysis what results were gleaned for Seroquel versus chlorpromazine.
Q. You don't see any checks or any Xs; right?
A. No, I don't.
Q. That's good. So, at least according to the table, Seroquel never won. You don't have any checks; right?
A. I've already said that I don't know whether this is an official document. It's eight years old. I've never seen it. And this could be the view of one person. It might have no widespread statistical validity. You are asking me to guess based on a document I've never seen if Seroquel on this data --
Q. Go ahead.
A. -- is less or more

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effective than chlorpromazine when it's not even marked in the document.
Q. By the way, Dr. Wayne Macfadden was U.S. medical director for Seroquel, was he not?
A. I don't know what his title was.
Q. You know who he is?
A. I think I met him once.
Q. He would have far more knowledge about the clinical studies than you, wouldn't he?
A. Because he was in the clinical function, he'd probably have more intimate knowledge of the studies, correct.
Q. Let's go down to Risperdal. Tell me, according to Table 1, where Seroquel beat Risperdal.
A. It looks like on this analysis in this paper it seems to suggest that risperidone has more efficacy on these measures.
Q. Thank you, sir. Other

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typicals, where did -- in this analysis in Table 1, where did Seroquel win?
A. You know, I'm not being difficult, but I really don't see the point in answering the question because I don't even know what other typicals are. I think it's a total waste of time having that conversation. It could be anything.
Q. Okay. Well, sir, I just don't, and we will let somebody else determine whether it's a total waste of time.
A. So do you know what those products are?
Q. Yes, sir, I actually do. I'm just saying --
A. Could you tell me and then that might help me?
Q. When you get to take my deposition, I will tell you whatever you want me to tell you.
A. Okay.
Q. I'm saying, according to

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to -- by the way, if you turn to the first page, it gives you the source of the data, and it's a meta-analysis that was conducted at AstraZeneca. It gives you the design of the trials. And then if we turn back to the conclusions on Page -- Bates Page 07, the last two numbers 07, do you see that? What do you -- right there. Do you see that, 07? They have a conclusion, do they not?

A. Yes, they do.

Q. Let me just read the conclusion to the jury and then ask you a question about it. "Conclusions. The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of equivalence is not ruled out." Did I read that correctly?

A. Yes, you did.

Q. Were you ever informed of that Technical Document No. 5 or its conclusions?

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A. I have told you twice already no.

Q. Okay. Do you think you maybe should have been informed of this information before you went around making claims of unsurpassed efficacy?

MR. AUSTIN: Object to form.

A. No, because I took my guidance from the head of clinical, the disclosure committee, and the SERM group.

By the way, how is equivalence different from unsurpassed?

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Do you really think you get to ask me questions? Is that what you think this process involves, that you get to ask me questions and I give you answers?

MR. AUSTIN: Don't argue with him. Just ask questions.

MR. ALLEN: He's arguing with me.

MR. AUSTIN: He is trying to answer your question.

THE WITNESS: I'm trying to answer your question.

BY MR. ALLEN:

Q. Well, let me ask, since you asked me a question, let me ask you a question: "Unsurpassed," "unsurpassed," what does that mean?

A. It means --

Q. Nobody is better; right?

A. It means equivalent.

Q. So if I really -- I'm trying to think of something. If I tell somebody that I went to a track meet and I saw an athlete that has been unsurpassed, I mean he was -- her, let's say her. Her ability to do the broad jump and the high jump and the relays were unsurpassed, and I was just so impressed and I go and tell you it was unsurpassed, you believe that means I'm saying she was equivalent to everybody

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else at the meet?

A. Possibly, yes. That's the correct grammar. Possibly, yes. She was possibly better; she was possibly equivalent.

Q. And if I come home and -- your child, you said, is 5 years old?

A. I have got two.

Q. How old are they? Mine are 22, 20, and 17. How old are yours?

A. 3 and 5.

Q. When your child comes home from school let's say from first grade and says, "Daddy, I" -- well, I don't think first grade. And your child may be smart because you are smart. So let's just go to fifth grade. Go to fifth grade. "Daddy, my grade in my English class was unsurpassed." What are you going to say, "Congratulations. You made the same grade as everybody else"?

MR. AUSTIN: Object to form.

BY MR. ALLEN:

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Q. Is that what you are telling this jury, is "unsurpassed" means the same?
A. Yes, it does, it means the same as or better. That's exactly what it means.
Q. So -- that's exactly what it means. So when AstraZeneca -- I'm glad to know this. This is interesting and I'm glad we're getting this out here. So when AstraZeneca made the claims of unsurpassed efficacy in regard to Seroquel, what they were meaning to say was, "We are just the same as everybody else"; is that right?
MR. AUSTIN: Object to form.
A. No, but I think we were incredibly careful with the use of grammar to depict what the clinical studies showed and concluded.
Q. You were trying to be tricky?
A. No. We were being incredibly precise and using the correct

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language. Of course, the language varied from country to country and label to label. The global impression from the safety and efficacy review group was our efficacy was unsurpassed.
Q. And you said in order to use that language, using your words, you were being incredibly careful; is that right?
A. No, I didn't. I said "incredibly precise."
Q. "Incredibly precise"; is that right?
A. Yes.
Q. All right. So if somebody understood the term "unsurpassed efficacy" to mean that you were better than others, they were just being incredibly what, dumb?
A. No. We would never make a claim without showing supporting documentation. So, for example, in the U.S., the doctor could read the label, he could read the FDA approval, and he

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could see the total span of facts.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'm not asking about the label and I'm not talking about the FDA approval. I'm talking about what you've called at various points during this deposition a slogan or a phrase used in regard to Seroquel, and that was unsurpassed efficacy. Are you telling this jury honestly under oath that you were being so incredibly precise in the marketing of Seroquel that "unsurpassed efficacy" really meant that "We were the same as everybody else"? Is that what you're telling this jury?
A. No. I'm saying that we chose that word to explain the fact that in the studies that we had done, our efficacy was unsurpassed when used in the right patients in the right dose in the right population. You can read a document like this without the context

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and it would be easy to be misunderstood about the total conclusion for what we say about Seroquel. That's why we have a SERM process.
Q. What document did you hold up?
A. That was the document you just gave me.
Q. Well, tell the jury what it was. You held it up. I was through with that document but I -- but what was the document you just held up?
A. This was Exhibit No. 48, which was from 2000, which was in -- between some technical people which was never signed, so it may not have been official, and was just one of a gigantic data set for Seroquel.
Q. Yes, sir. That's -- you chose to get back into it. I'll deal with it. 48, "Conclusions. The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of

EXHIBIT
6

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From: Birkett, Geoff

Sent: Tuesday, March 04, 2003 7:44 PM

To: Bierczynski, Vicky B

Subject: FW: Schizo SSF 3.04

Attachments: Schizo SSF 3.04.ppt

pls do neat colour copy for tomorrow

-----Original Message-----

From: Wilkie, Alison M

Sent: Tuesday, March 04, 2003 2:28 PM

To: Birkett, Geoff

Cc: Bierczynski, Vicky B

Subject: Schizo SSF 3.04

Birkett
EXHIBIT NO. 2
AMC 4/24/08

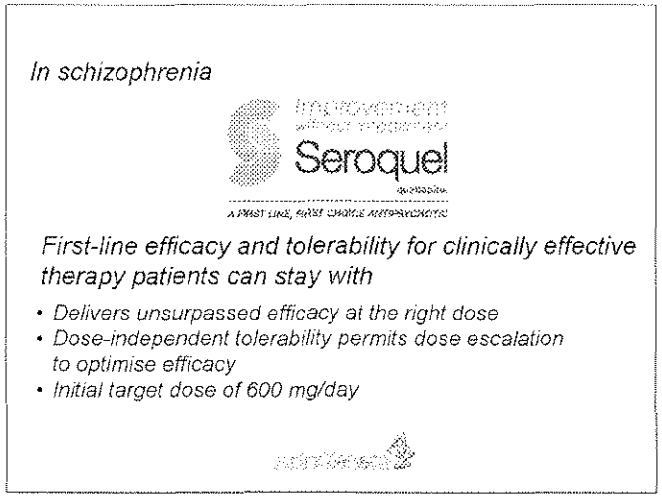
Geoff

Here is the 'tweaked' version for John tomorrow - please let me know if you have any questions.

S339-E00007330.tif

thanks

Alison



The following pages represent a **core detail flow** and **backup data** that support our current position for Seroquel in the treatment of schizophrenia.

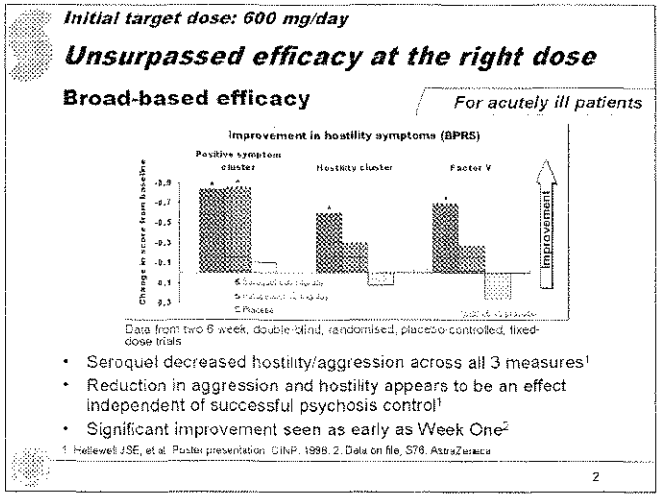
The detail flow

The detail flow presents a succinct summary of the strongest data from our best studies to support Seroquel as the unsurpassed clinical effectiveness at the right dose with:

- Dose-independent tolerability that permits dose escalation to optimise efficacy
- At the right dose—starting with an initial target of 600 mg/day—Seroquel offers unsurpassed clinical effectiveness
- The target 600-mg/day dose is flagged on every page showing efficacy data

Backup data

Backup data are supplied so that local markets can either expand on the data in the core detail or substitute data approved for marketing purposes.



The symptom spectrum for schizophrenia includes aggression and hostility, which need to be controlled without worsening other primary symptoms.

Key communication

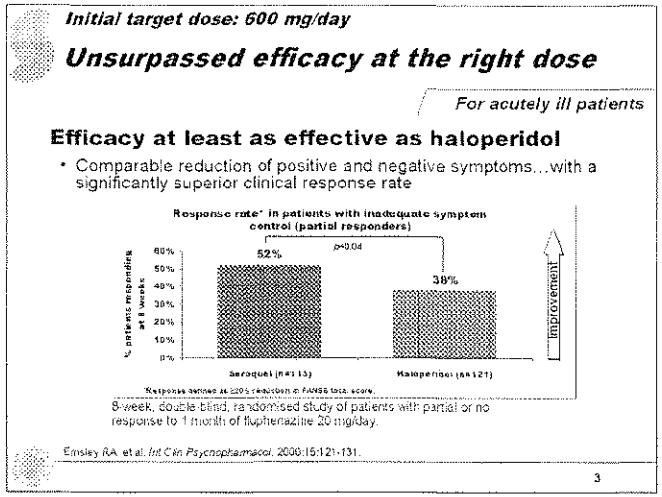
In addition to managing positive and negative symptoms, Seroquel effectively controls aggressive/hostile symptoms.

On this page

- The graph shows Seroquel efficacy in controlling symptoms compared to haloperidol and placebo
- The second bullet notes that, although Seroquel controlled positive and negative symptoms in these studies, improvement in aggression/hostility was an independent effect
- The third bullet emphasises the rapid onset of symptom control

About the study

- Data from two 6-week, well-controlled trials. One trial compared 5 different doses of Seroquel to haloperidol 12 mg/day or placebo. The other trial compared low doses (up to 250 mg/day), and high doses (up to 750 mg/day) to placebo
- Seroquel 600 mg/day was associated with the most consistent improvement
- Seroquel produced greater improvement than haloperidol, but differences were not statistically significant. In addition, changes vs placebo were significant at certain points for Seroquel, but not for haloperidol



Seroquel and haloperidol have been compared in a number of studies. The Emsley study compares these agents in patients with partial treatment failure on other medication.

Key communication

Head to head with haloperidol, Seroquel offers the same—or better—efficacy, and the added advantage of a significantly better clinical response.

On this page

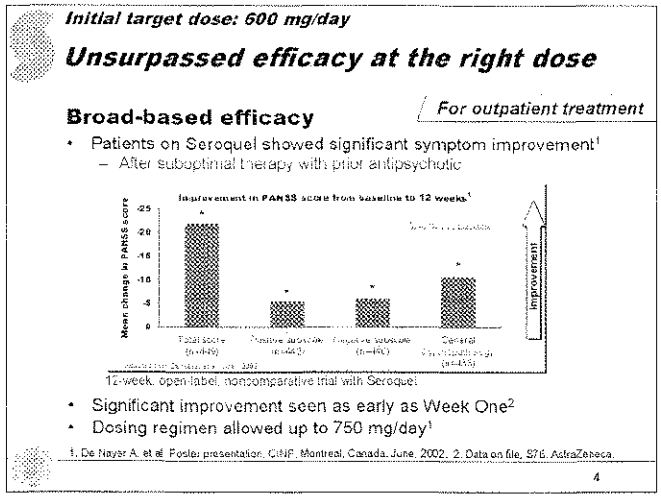
- The graph shows that Seroquel had a significantly better response rate (patients with a ≥20% reduction in PANSS score) than haloperidol
- The bullet highlights the Seroquel advantage—equal efficacy, superior response

About the study

- An 8-week, well-controlled trial of 288 patients who had partial response to typical antipsychotics and no response to fluphenazine
- Seroquel showed marked reduction in PANSS scores greater at Week 8 and Week 12 than haloperidol, although these scores did not reach significance
- More patients taking Seroquel also showed CGI Severity of Illness score ≤3

CGI: Clinical Global Impression. PANSS: Positive and Negative Syndrome Scale.

3



The detail flow starts with efficacy. Seroquel efficacy has been proven in numerous well-controlled clinical trials to control a range of schizophrenia symptoms, including 2 of the most critical kind—positive and negative symptoms.

Key communication

Seroquel significantly improved key symptoms of schizophrenia in patients unsuccessfully treated with another antipsychotic medication

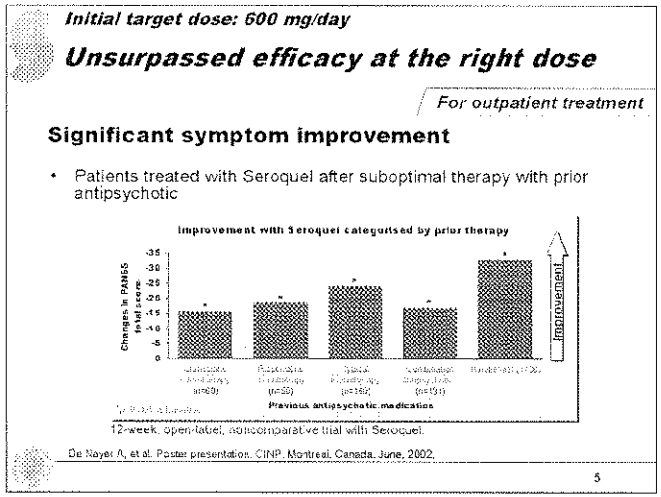
On this page

- This graph shows data from the SPECTRUM study, illustrating the change in PANSS scores for all patients
- *The next page shows improvement categorised by prior suboptimal treatment*
- The second bullet emphasizes rapid onset of improvement—within 1 week
- The third bullet reinforces efficacy at the right dose

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel

PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



The advantages of switching patients to Seroquel from current therapy support its use as a first-line choice.

Key communication

Seroquel improves efficacy, no matter what antipsychotic agent was used prior. So why not start patients on Seroquel, and get the right efficacy from the beginning?

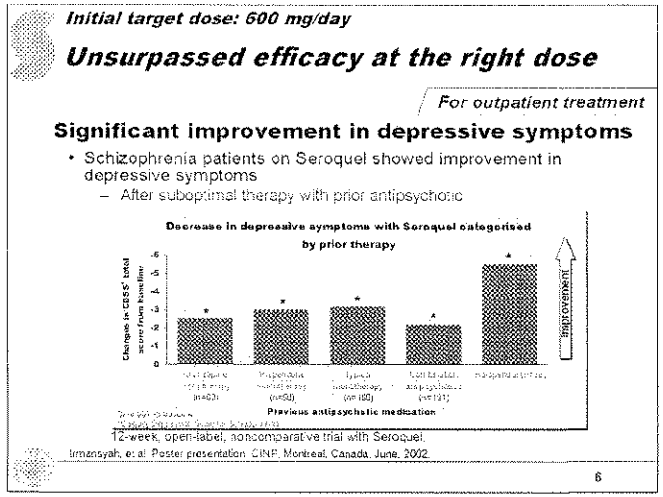
On this page

- This graph demonstrates that, no matter which antipsychotic a patient was switched from, Seroquel provided symptom improvement (as measured by PANSS)

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- Study results show that patients who were started on Seroquel due to partial or no response on previous medication showed symptom improvement and a reduction in EPS side effects
- Similarly, patients who were started on Seroquel because of intolerance to the side effects of their previous medication not only showed a reduction in side-effect incidence, but an improvement in efficacy

EPS: Extrapyramidal symptoms. PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



An antipsychotic that can help treat depression, as well as positive, negative, and other symptoms of schizophrenia, is a valuable treatment choice.

Key communication

Improvement with a switch to Seroquel includes reduction in depressive symptoms.

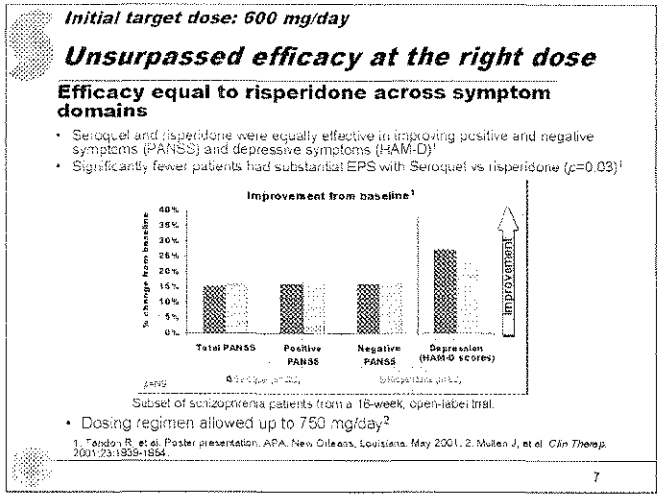
On this page

- This graph demonstrates that, no matter what antipsychotic patients were switched from, Seroquel provided improvement in depressive symptoms

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel
- While improvement was seen regardless of whether patients were evaluated as depressed when they started Seroquel, improvement was especially noticeable in patients classified as depressed at baseline

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Data from QUEST compare the symptom relief of Seroquel and risperidone.

Key communication

Seroquel improved positive, negative, and depressive symptoms significantly better than risperidone.

On this page

- The graph, from the QUEST study, shows improvement in PANSS scores and depressive symptoms in a subset of patients with schizophrenia
- The bullet below the graph notes that dosing went as high as 750 mg/day in this study

About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- A subset of patients with schizophrenia was also analysed

HAM-D: Hamilton Rating Scale for Depression. PANSS: Positive and Negative Syndrome Scale.
QUEST: Quetiapine Experience with Safety and Tolerability.

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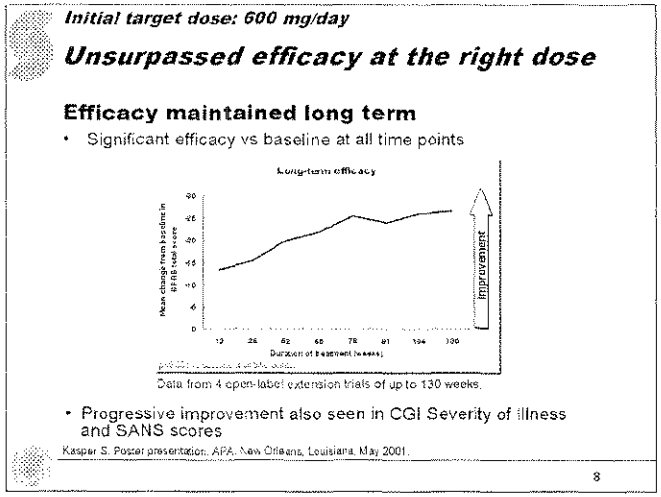


A chronic condition like schizophrenia requires treatment that stays effective long term.

Key communication

Seroquel maintains effective control of symptoms for the long term.

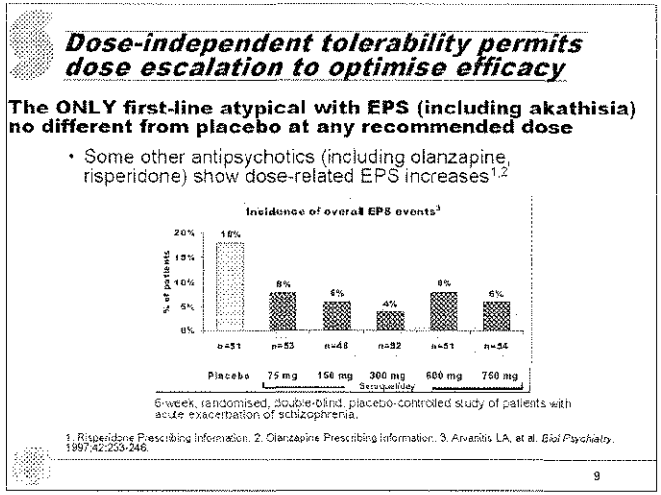
On this page

- The graph plots improvement in total BPRS score (which includes positive and negative symptom measures, as well as 16 other items) over 130 weeks
- The second bullet highlights that, in addition to improving BPRS score, Seroquel therapy improved severity of illness, as measured by CGI, and negative symptoms, as measured by SANS

About the study

- Data analysis for 674 patients in 4 open-label extension trials lasting up to 130 weeks
- Efficacy and tolerability were assessed

BPRS: Brief Psychiatric Rating Scale. SANS: Scale for the Assessment of Negative Symptoms.
CGI: Clinical Global Impression.



After efficacy, the detail flow reinforces the well-known Seroquel safety profile, starting with EPS—a side effect of many antipsychotics that interferes with patients' daily function and compliance. Placebo-level EPS is one of the best-known attributes of Seroquel therapy.

Key communication

Seroquel is the only first-line atypical with EPS no different than placebo at any recommended dose.

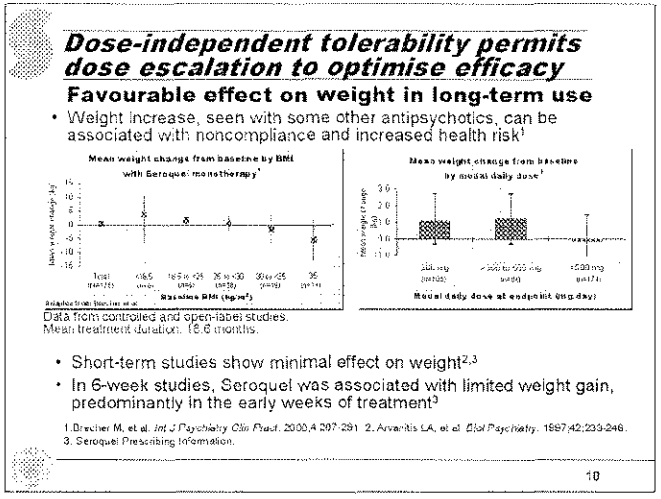
On this page

- The graph shows that incidence of EPS barely changed across Seroquel doses in the study, from the lowest dose (75 mg/day) to the highest dose (750 mg/day)
- The bullet refers to the risperidone and olanzapine PIs, which show increased EPS incidence with increasing doses
- *Other EPS-related data can be found in the backup section*

About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- EPS evaluation was measured by SAS (modified to include akathisia) and AIMS
- Incidence of EPS-reflective events: Seroquel—4-8%, placebo—16%, haloperidol—37%

AIMS: Abnormal Involuntary Movement Scale. EPS: Extrapyramidal symptoms. SAS: Simpson-Angus Scale.



Weight gain is a side effect clearly associated with certain antipsychotics, and can be a primary reason for patient noncompliance.

Key communication

Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain, either in the short or long term or across the recommended dosing range.

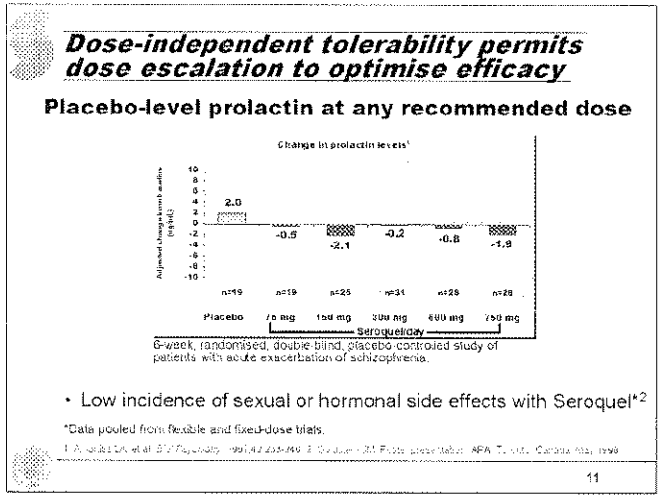
On this page

- The left-hand graph evaluates weight gain over a mean treatment duration of 18 months in patients grouped by baseline BMI category
- The right-hand graph shows weight change categorised by 3 dosing ranges
- Overall, there was almost no mean change in weight. Interestingly, in underweight patients (BMI ≤18), there was beneficial weight gain, while the most overweight groups (BMI 30-35) lost weight

About the study

- Long-term weight-change data for 427 patients were pooled from controlled and uncontrolled studies as well as from their open-label extensions
- In these studies, Seroquel monotherapy was the only antipsychotic treatment allowed

BMI: Body Mass Index.



Abnormal prolactin levels are a common adverse event caused by antipsychotic medication.

Key communication

As with EPS, prolactin levels in patients taking Seroquel are no different than with placebo across the dosing range

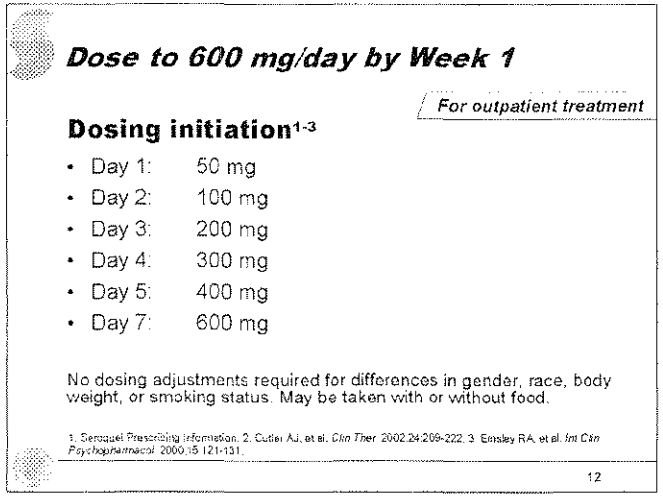
On this page

- The graph shows the minimal change in prolactin levels with Seroquel treatment
- The bullet, from a study by Goldstein, confirms that placebo-level prolactin means minimal risk of sexual or hormonal dysfunction

About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- In contrast to Seroquel, the difference in prolactin levels between placebo and haloperidol was significant

EPS: Extrapyramidal symptoms.



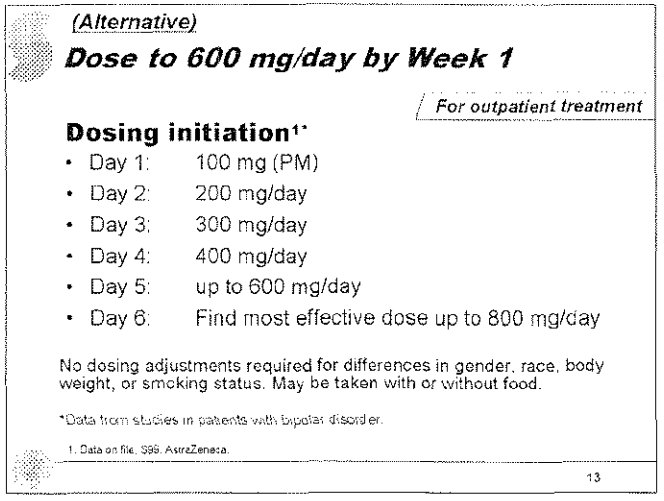
Standard dosing initiation achieves the initial target dose of 600 mg/day by Day 7.

Key communication

Dosing to 600 mg/day is simple and fast.

On this page

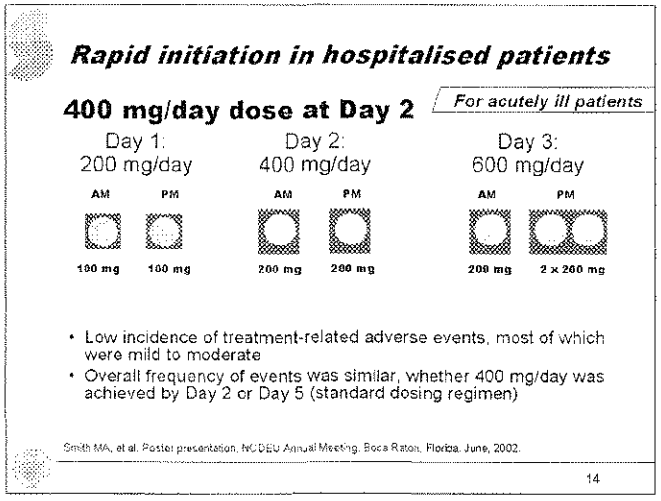
- Physicians are familiar with the dosing schedule from the Prescribing Information for Seroquel



The "four by four" dosing approved for treatment of bipolar mania gets patients to 600 mg/day at Day 5.

Key communication

An accelerated dosing schedule for Seroquel has been proven safe and effective in clinical studies.



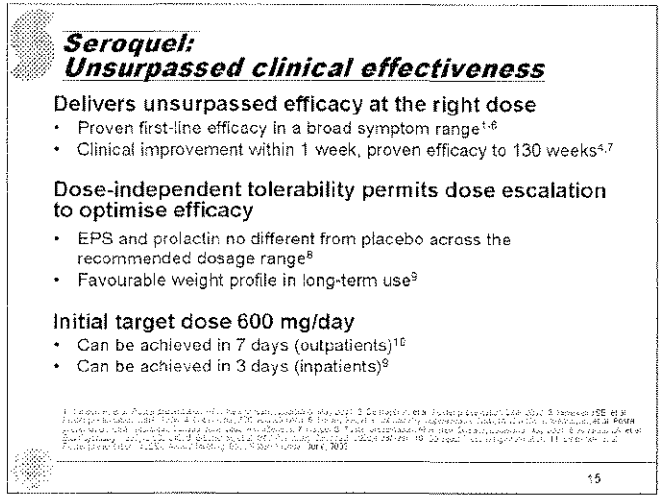
For acutely ill patients, an even more rapid target dose initiation has been shown to have a comparable tolerability profile to traditional dosing schedules.

Key communication

Seroquel can be dosed up to 600 mg/day in fewer than the standard 5 days with safety and tolerability.

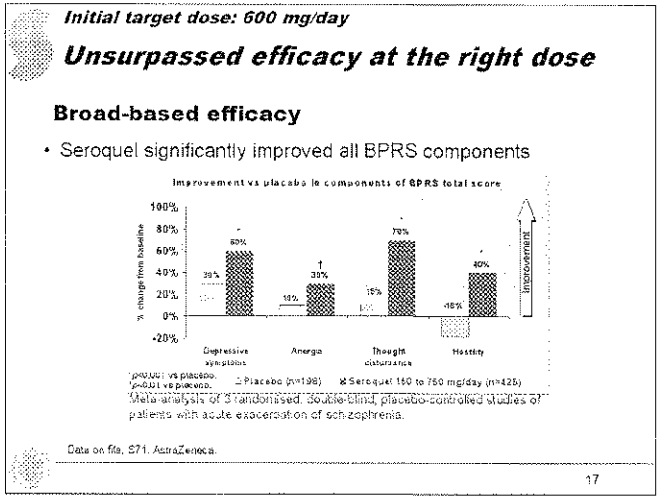
About the study

- This was a 5-day, multicentre, double-blind tolerability/safety study of 69 acutely ill schizophrenia patients randomised to 1 of 3 titration arms
- Patients were dosed to 400 mg/day of Seroquel in 5, 3, or 2 days. Patients were hospitalised during their 2-day washout and 5-day treatment periods
- Frequency of adverse events was similar between the 3 groups. Treatment-related events were few, and most were mild to moderate
- Less than 15% of patients experienced somnolence, with the fewest (8%) in the 2-day titration group
- Laboratory values and vital signs were also similar amongst the treatment arms, including for blood pressure and pulse measurements



This page summarises the key communications in the core detail.

Back-up slides



Additional material on efficacy includes secondary symptoms of schizophrenia.

Key communication

Seroquel effectively manages a wide range of symptoms.

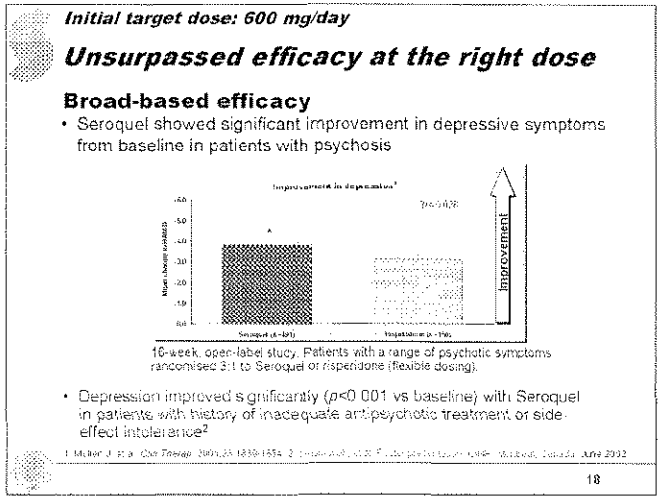
On this page

- Seroquel efficacy in controlling 4 individual symptoms comprising the BPRS, with significant differences vs placebo for each

About the study

- Meta-analysis of three 6-week, well-controlled published studies
- Dosing regimens were different for each study

BPRS: Brief Psychiatric Rating Scale.



Data from QUEST support the proven relief of depression with Seroquel.

Key communication

In patients treated for a range of psychosis symptoms, Seroquel improved depressive symptoms significantly better than risperidone.

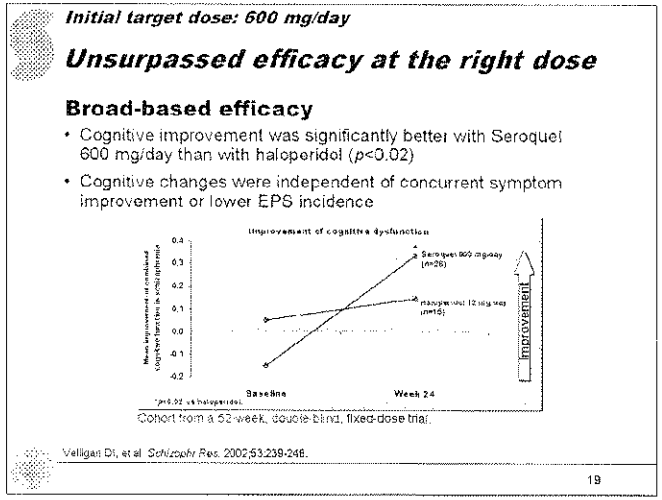
On this page

- The graph, from the QUEST study, shows improvement in depressive symptoms in all patients in the study (ie, all forms of psychosis), measured by change in HAM-D scores
- The bullet below the graph refers to the SPECTRUM study, in which patients with schizophrenia who were unresponsive or intolerant to other antipsychotics were started on Seroquel monotherapy

About the studies

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- 641 patients from QUEST were evaluated for depressive symptoms
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel flexible dosing

HAM-D: Hamilton Rating Scale for Depression. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Improvement in cognitive function can help patients recapture functions critical to basic day-to-day tasks.

Key communication

Seroquel 600 mg/day improved cognitive function significantly better

than haloperidol.

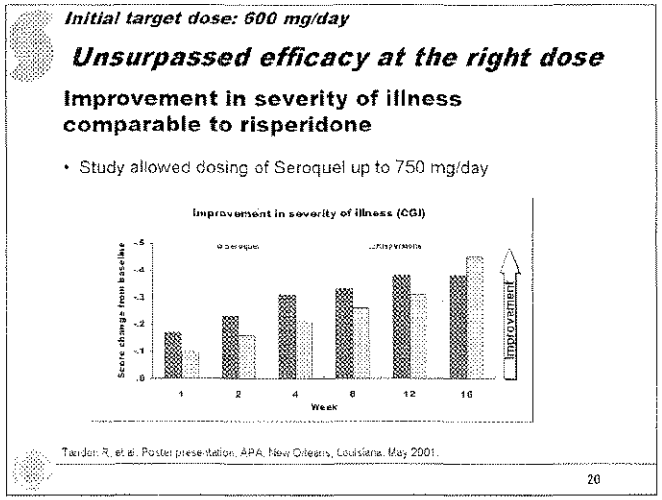
On this page

- The graph and first bullet show the difference between Seroquel and haloperidol in restoring some degree of cognitive function
- The second bullet points out that cognitive improvement was independent of the other benefits of Seroquel (improvement in other symptoms, less incidence of EPS)

About the study

- This was a cohort from a 52-week study of patients on fixed-dose Seroquel, haloperidol, or placebo

EPS: Extrapyramidal symptoms.



Data from QUEST support the efficacy of Seroquel compared to risperidone.

Key communication

Seroquel and risperidone are equally effective in symptom relief.

On this page

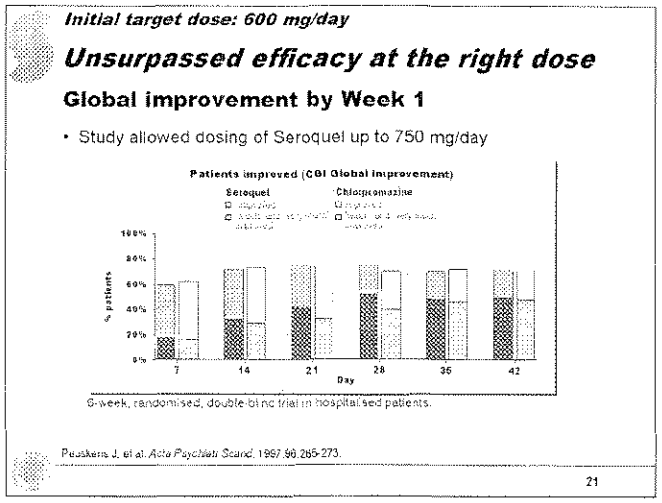
- The graph, from the QUEST study, shows global improvement
- The same study showed that Seroquel produced less substantial EPS than risperidone

About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone

CGI: Clinical Global Improvement. EPS: Extrapyramidal symptoms. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.

20



The CGI scale is a well-known, well-accepted measurement of overall symptom improvement.

Key communication

Global improvement—particularly in patients who were "very much" improved—can be seen as early as 1 week and continues to increase throughout treatment.

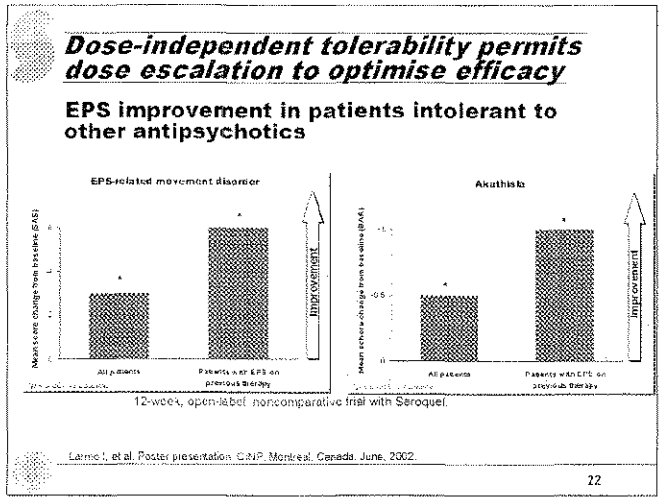
On this page

- The graph shows improvement at Day 7, with the ratio of patients "much" and "very much" improved continuing to grow over the 42 days of the study

About the study

- This was a 6-week study of patients hospitalised with acute exacerbation of schizophrenia
- Tolerability was also evaluated in this study. Fewer patients in the group on Seroquel had parkinsonian symptoms or akathisia vs those in the chlorpromazine group. Elevated prolactin dropped significantly with Seroquel vs chlorpromazine

CGI: Clinical Global Impression



Data from the SPECTRUM study show that a switch to Seroquel can reduce EPS caused by other antipsychotics.

Key communication

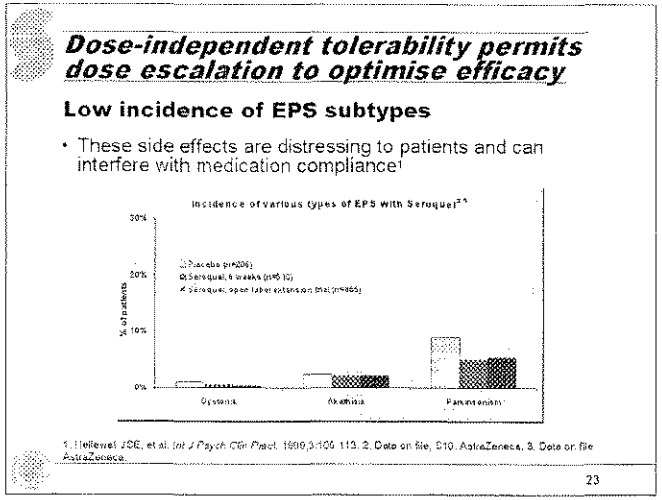
To avoid the EPS caused by other antipsychotics, why not start Seroquel first?

On this page

- The graphs, from the SPECTRUM study, show that the incidence of 2 EPS categories—movement disorder and akathisia—decreased in patients switched to Seroquel from other antipsychotics
- Akathisia is a subset of EPS of particular concern to physicians

- **About the study**
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- A total of 506 patients were evaluated for safety
- EPS was measured by the SAS (movement disorders) and BAS (akathisia) scales

EPS: Extrapyramidal symptoms. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



More support for placebo-level EPS, by subtype.

Key communication

Seroquel shows no more incidence of EPS than placebo when symptoms are broken down by subtype.

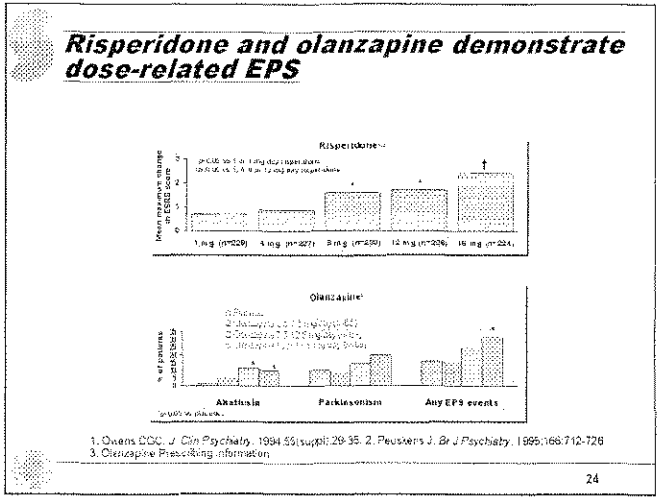
On this page

- 2 studies confirm the Seroquel safety profile

About the studies

- Data on File S10 showed that Seroquel showed no difference vs placebo in EPS subtypes across a 75-mg to 150-mg dosing range
- (Second DOF info to come from client)

EPS: Extrapyramidal symptoms.



EPS data for risperidone and olanzapine confirm the difference in safety profiles between these atypicals and Seroquel.

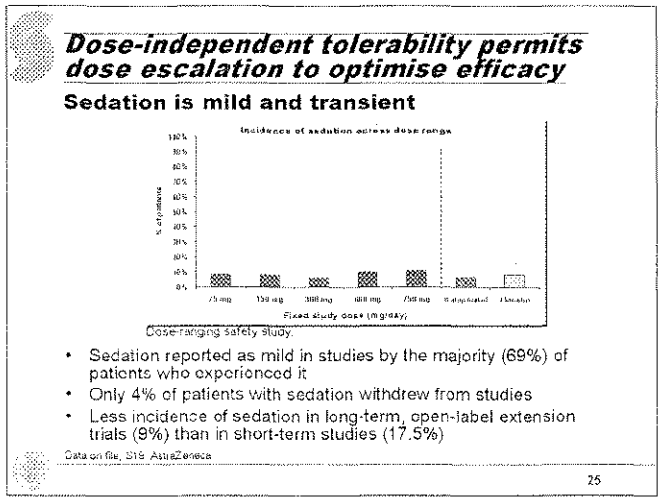
Key communication

Unlike Seroquel, both risperidone and olanzapine show dose-related increases in EPS.

On this page

- These graphs expand on the points made in the core detail piece and backup

EPS: Extrapyramidal symptoms.



Reports of the impact of sedation with Seroquel are greatly exaggerated.

Key communication

Sedation associated with Seroquel therapy is transient and mild across the dosing range

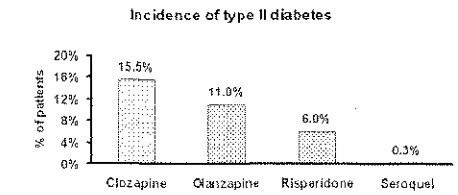
On this page

- A dosing study shows sedation incidence hardly increases, even at higher doses, and is comparable to haloperidol

About the studies

- Data on File S19 is from uncontrolled, placebo-controlled, and haloperidol-controlled studies of almost 3,000 patients taking Seroquel

Type II diabetes associated with atypical antipsychotic use



Cross-sectional study of 398 patients

Data on file AstraZeneca Canadian Guidelines on the Treatment of Diabetes 1999

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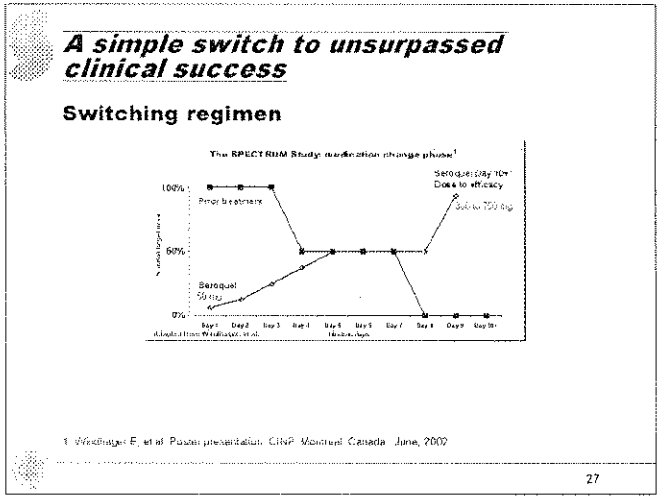


Starting patients who are taking another antipsychotic on Seroquel means simply cutting the current medication in half and increasing Seroquel in a few easy steps.

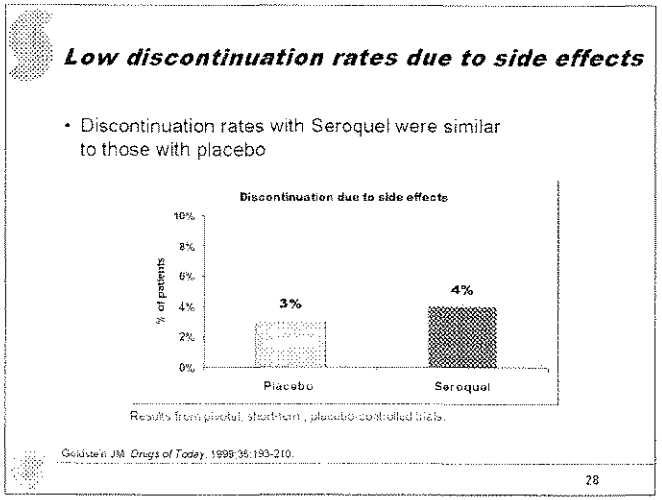
Key communication

Switching patients to Seroquel is simple.

On this page

- The schematic shows the switch protocol from the SPECTRUM study, in which patients were switched to Seroquel from a variety of other antipsychotics

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Seroquel tolerability is supported by its low discontinuation rates.

Key communication

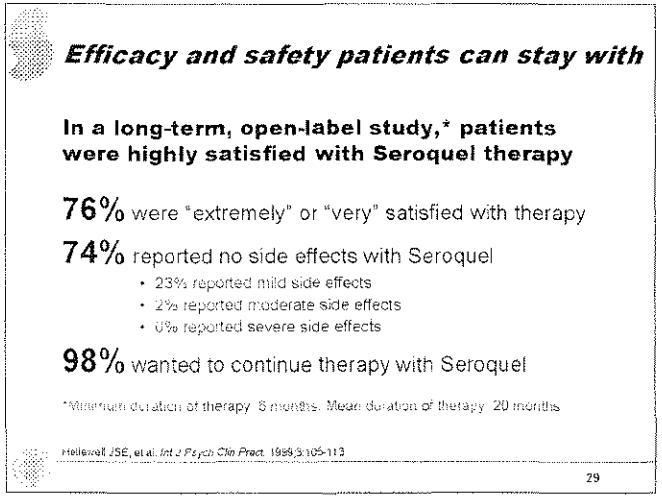
The percentage of patients stopping therapy with Seroquel due to side effects were essentially the same as with placebo.

On this page

- Simple and compelling evidence of Seroquel tolerability

About the study

- Pooled data from short-term trials



The efficacy and unique tolerability profile of Seroquel add up to patient satisfaction, providing therapy that patients can stay with long-term.

Key communication

The great majority of patients were highly satisfied with long-term Seroquel efficacy and tolerability. Almost all expressed interest in continuing therapy with Seroquel.

On this page

- The numbers link patient-reported satisfaction with efficacy and tolerability, with the conclusion that virtually all of them would continue therapy

About the study

- 129 patients from 12 countries who had been on Seroquel for at least 6 months and currently in open-label studies were asked to complete a questionnaire about satisfaction with therapy
- Mean treatment duration with Seroquel was 19.9 months, with 38% of patients on treatment for 31 to 42 months
- The most common characteristics patients reported that they liked about Seroquel were lack of side-effects or improvement in side effects caused by other medications
- 96% of patients who expressed a medication preference indicated a preference for Seroquel over previous antipsychotics for both efficacy and tolerability

EXHIBIT 8

ROUGH DRAFT{PRIVATE

}

QUETIAPINE

Joyce G. Small, M.D.[1]

Department of Psychiatry

Indiana University School of Medicine

Larue D. Carter Memorial Hospital

2601 Cold Spring Road

Indianapolis, IN 46222-2202

Telephone: 317/941-4000

FAX: 317/941-4014

1. Professor of Psychiatry

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Wilkins.

QUETIAPINE

Introduction:

Seroquel (quetiapine fumarate, ICI 204,636), which was ~~developed~~ discovered in 1984 in the Zeneca (formerly ICI)Wilmington DE laboratories, is a dibenzothiazepine derivative with preclinical indications of antipsychotic activity without neurological side effects or elevations in prolactin. The structural formula is shown in Figure 1. Quetiapine exhibits binding properties similar to clozapine(1,2). Receptor data in animals showed quetiapine's greater affinity for 5-HT2 and 5-HT6 relative to D2 receptors. ~~although recent human evidence suggests that D2 binding may have been underestimated~~. Like clozapine, ~~Quetiapine, clozapine and other atypical neuroleptics occupy high levels of brain D2 receptors but are~~ quetiapine is loosely bound and readily displaced from the D2 receptor, particularly in the striatum(3), providing a mechanism for its low EPS liability~~.~~ It is selective for the A10 mesolimbic but not A9 nigrostriatal dopamine neurons. Unlike clozapine quetiapine has minimal affinity for M1 or D4 but binds strongly to the sigma receptor(4).

In this review clinical data from the pivotal placebo controlled

studies preceding the 1997 marketing of Seroquel and additional reports will be considered under headings of clinical efficacy, safety and tolerability, adverse events including movement disorders, laboratory abnormalities, pharmacokinetics and drug interactions, and therapeutic potential.

Clinical Efficacy:

Several thousand patients have been treated with quetiapine. Although all studies required DSM-III-R diagnoses of acute exacerbation of chronic or subchronic schizophrenia, all subjects typically had long histories of psychotic illness, multiple hospitalizations and previous treatment with standard and sometimes atypical antipsychotic drugs as well. Thus despite manifestations of acute psychosis, most patients could be regarded as chronically ill and relatively treatment resistant. Many of the trials were conducted in tertiary-care teaching centers. Moreover, women of child bearing potential were mostly excluded as were those unwilling to give consent. Hence they were a select group not truly representative of patients routinely encountered in clinical practice. Another consideration is that all conclusions available thus far are derived from industry supported studies without the benefit of confirmation by independent investigators(5).

There have been three placebo controlled pivotal Phase II and III

trials of quetiapine that utilized a substantial number of patients, randomized double-blind treatment assignment and trial durations of six weeks. The first was by Borison et al.(6) who studied 109 patients. Quetiapine was generally superior to placebo in an average dose of 307 mg. Small et al.(7) published results of a multicenter trial of 286 patients on low or high dose quetiapine OR placebo. The average low dose of 209 mg was no better than placebo but the mean high dose of 360 mg was superior to placebo. Arvanitis et al.(8) studied multiple doses of quetiapine compared with haloperidol and placebo. Dosages ranging from 150 to 750 mg were superior to placebo and equivalent to 12 mg of haloperidol. The lowest dose of 75 mg was ineffective. Another study by Peuskins and Link (9) compared quetiapine to chlorpromazine in 201 patients. The two drugs were therapeutically equivalent in mean doses of 407 mg of quetiapine and 384 mg of chlorpromazine. More details about each of these studies follow:

In the Borison et al., study overall therapeutic efficacy favored quetiapine. Although there were statistically significant differences between the treatment groups ($p \leq 0.05$) in favor of quetiapine at various times throughout the trial, differences at end point were not significant on the Brief Psychiatric Rating Scale (BPRS)(10) total score ($p=0.07$) or the anxiety/depression, anergia, thought disturbance, and hostile/suspiciousness factors. Differences in the BPRS positive

symptom cluster approached significance (p=0.06). The end of study Clinical Global Impression (CGI) rating (11) was likewise not significant (p=0.07). Statistical comparisons included all randomized patients who had efficacy data for at least one time interval after baseline with last observation carried forward (LOCF) for determinations at end point. More significant differences were observed earlier in the study in the quetiapine treated patients who improved steadily throughout the six week period whereas placebo subjects remained unchanged. BPRS total scores were significantly different on days 14, 28, and 35 as was the positive symptom cluster. Factor 3 - thought disturbance - was significantly better for quetiapine on days 28 and 35. CGI ratings showed significant differences between treatments on days 21, 28, and 35. The Scale for Assessment of Negative Symptoms (SANS) (12) showed significant group differences from day 21 onwards.

In the study by Small et al., comparing low and high dosage ranges of quetiapine with placebo, the low dose group and placebo were equivalent on global ratings and positive and negative symptoms. The high dose group at end point was significantly more improved on the CGI, the BPRS positive symptom cluster, and the SANS but not the Positive and Negative Syndrome Scale (PANSS)(13). These conclusions were also drawn from LOCF analyses.

Arvanitis et al., studied five fixed doses of quetiapine compared

with 12 mg of haloperidol and placebo. The lowest dose of 75 mg was not different than placebo whereas the quetiapine and haloperidol groups were equivalent at end point for the total BPRS scores and the positive symptom cluster and the CGI. Only the 300 mg dose of quetiapine and placebo scores were significantly better than haloperidol on the SANS. Based on this experience and the previous studies the optimal doses of quetiapine appear to range from 300 to 600 mg. However preferred amounts for management of primary negative symptoms and cognitive impairments to promote the best possible quality of life remain to be ascertained.

Additional randomized double blind trials without placebo conditions have been published. Peuskens and Link compared flexible doses of quetiapine with chlorpromazine showing that quetiapine was as effective as chlorpromazine on measures of both positive and negative symptoms. Sixty-five percent of quetiapine patients and 53% of chlorpromazine subjects achieved at least a 50 percent improvement in total BPRS total score at some point during the study, a statistically significant difference ($p = 0.04$) favoring quetiapine. In other trials dosing frequency was examined comparing two or three times daily schedules. Outcomes with bid and tid dosing were equivalent, corresponding with time courses of PET studies of decline in D2 and $5HT_2$ receptor occupancy but not plasma half-life(14).

Other evidence of therapeutic efficacy of quetiapine can be inferred from uncontrolled studies and case reports. Favorable results in two patients with psychosis and Parkinson's Disease were reported in which mental symptoms improved and Parkinsonism was not adversely affected(15). Another study examined the effectiveness of quetiapine in psychotic geriatric patients(16). An interim analysis was done in 150 patients after twelve weeks of treatment with average dosages of 75 to 100 mg. BPRS total scores and CGI global ratings improved progressively during the course of the trial with significant decreases from baseline. Results were comparable in patients with idiopathic or organic psychoses.

Cognitive impairment is another core feature of schizophrenia which may be benefited more by atypical than standard neuroleptics(17). Performance by schizophrenics and normal controls on a continuous performance test was studied before and after quetiapine therapy in the patients(18). They were significantly worse than normals at baseline but by the end of two months of treatment did not differ significantly from controls. The trial involved 10 patients who received quetiapine as part of other multicenter trials and a comparison group of twelve matched normal volunteers. More comprehensive trials with full neuropsychological test batteries have yet to be reported with quetiapine.

Since marketing of quetiapine abstracts, letters and case reports

about individual experiences have appeared at scientific meetings, in journals and on the Internet. Favorable results were reported in an adolescent with childhood onset schizophrenia who had not responded satisfactorily to other atypical neuroleptics i.e., risperidone and olanzapine(19). Cognitive improvement accompanying treatment with Seroquel was described in a man with chronic schizophrenia(20). Positive comments have appeared on the Internet, mentioning advantages with quetiapine mostly due to fewer side effects(21). Recent presentations have included therapeutic benefits in Alzheimer's disease associated with psychosis,(22) in adolescent patients,(23) and in schizophrenic patients displaying hostility, aggressive behavior and affective symptoms(24). Surveys of caretaker and patient satisfaction indicated a high rate of acceptability of atypical neuroleptics in general and quetiapine in particular with improved quality of life(25,26). Another study was presented indicating beneficial results with quetiapine in Parkinsonian patients on both psychotic and motor abnormalities(27). Comparative studies of quetiapine with other atypical antipsychotic drugs are beginning to appear. An open-label four month trial comparing quetiapine and risperidone in 751 outpatients (28) showed improvement on both drugs with advantages for quetiapine on depression ratings and the CGI. There were no statistically significant differences on ratings of positive or negative schizophrenic symptomatology.

To summarize the data on therapeutic efficacy: relief of positive symptoms appears comparable to standard neuroleptics, primarily haloperidol. Effects on negative symptoms are less robust but they appear to resolve to a greater extent than with placebo or standard neuroleptics. Data on cognitive dysfunctions and quality of life issues are sparse. It must be kept in mind that the bulk of the information about efficacy is limited to six weeks of treatment with few controlled observations for longer time periods. Moreover information in schizoaffective and bipolar disorders, the elderly and pediatric populations and medically compromised patients is minimal and no data are published to date on first episode or refractory schizophrenia.

Safety and Tolerability:

Quetiapine has a good overall safety and tolerability profile with few patients discontinuing from studies due to adverse effects. It has an especially low incidence of extrapyramidal side effects (EPS) with values comparable to placebo and no evidence of a dose response curve. This was also reflected in the minimal use of concomitant anticholinergic medications. The primary reason for early dropouts from pivotal studies was treatment failure as would be expected in chronically ill, hospitalized schizophrenic patients. Correspondingly, the most frequently reported adverse events were common accompaniments of schizophrenic exacerbations

such as agitation and sleep disturbances.

The controlled trials yielded similar adverse event profiles with quetiapine with most complaints rated as mild or moderate. Agitation, somnolence, and headache were the most commonly reported side effects. Somnolence was more common with quetiapine than placebo but similar for quetiapine and low to moderate doses of chlorpromazine. Postural hypotension was encountered infrequently with quetiapine in the placebo controlled trials, occurring three times more often with the chlorpromazine comparator. Other less frequently encountered events included constipation, dry mouth, and tachycardia. Case reports of quetiapine overdoses also attest to its safety(29,30). Sinus tachycardia and sedation were the major effects of acute overdosages from 4700 to over 10,000 mg which resolved uneventfully with supportive care.

Adverse Events:

There is a wide spectrum of potential adverse events with antipsychotic drug therapy. Neurological side effects are the major category which includes Parkinsonism, dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, seizures and epileptiform EEG features. Impaired cognition, psychotic, decompensation, abnormalities in mood, behavioral worsening and obsessive compulsive manifestations are other CNS effects. Further

all antipsychotics can produce adverse withdrawal symptoms if suddenly or rapidly discontinued with psychotic decompensation, cholinergic rebound, emergent dyskinesias, and general malaise. Early relapse may be more problematic with atypical than standard neuroleptics because of loose binding and rapid release from D2 receptor occupancy in the former(31).

Significant endocrinological abnormalities may develop due to hypogonadism produced by hyperprolactinemia with galactorrhea, menstrual irregularities, sexual dysfunctions and long term risks of osteoporosis, breast cancer and heart disease. Disturbances in glucose regulation may accompany atypical neuroleptic therapy. Asymptomatic deviations in thyroid function tests have also been reported. Weight gain is a common problem. Other side effects involve cardiovascular events such as prolonged QTc interval, postural hypotension, tachycardia and other arrhythmias. Decreased bowel motility, cholestatic jaundice and other gastrointestinal problems can occur. Transient elevations in hepatic transaminase activity have been observed, generally without clinical manifestations.

Unlike the case with clozapine, agranulocytosis and other hematologic abnormalities are not frequently associated with standard or other atypical antipsychotic agents. Nonetheless all of these drugs can impact adversely on multiple organ systems

giving rise to ophthalmologic, dermatologic, allergic and other complications.

Neurological Effects:

Extrapyramidal side effects (EPS) did not distinguish between quetiapine and placebo in the three placebo controlled trials cited previously as measured by Simpson-Angus Scale (SAS) (32) scores at endpoint. This was also reflected in the minimal use of anticholinergic agents for treatment emergent EPS. In the Arvanitis et al. study twelve percent of patients on quetiapine were given anticholinergic drugs for control of EPS compared to 14% on placebo and 48% on haloperidol. The incidence of akathisia measured by the Barnes Scale (33) was the same for quetiapine as with placebo. In the quetiapine - chlorpromazine comparison there were low levels of EPS in both treatment groups. Among the chlorpromazine subjects one patient was withdrawn because of an acute dystonic reaction and more anticholinergic medications were prescribed. Quetiapine and placebo Barnes scores tended to improve from baseline, more with higher quetiapine doses, whereas the haloperidol group worsened. It can be concluded that quetiapine rarely produces EPS. However two cases who experienced EPS with relatively low doses of quetiapine were reported on the Internet(21). One was an Asian woman and the other a man diagnosed as bipolar.

Seroquel has not been available long enough to ascertain its liability for producing tardive dyskinesia (TD). Judging from data on other atypical neuroleptics, the risk can be predicted to be substantially less than with standard neuroleptics. It is also not yet clear whether quetiapine will suppress abnormal involuntary movements. Likewise the risks of neuroleptic malignant syndrome are unknown although cases with several other atypical antipsychotic agents have been reported.

Seizures are another complication of neuroleptic therapy, particularly with clozapine(34). With some exceptions the incidence of seizures is directly proportional to the degree of sedation associated with the drug as well as other factors such as dosage and speed of titration, seizure threshold, concomitant medications, etc.(35). The incidence of seizures with clozapine has been reported as 1.1% whereas clinical trial data for olanzapine yielded 0.9%, risperidone 0.3% and quetiapine 0.8% (36). Epileptiform EEG features in association with clozapine treatment may warn of impending seizures if the dosage continues to increase. However they may also be a favorable prognostic sign(37).

Other research has involved quantitative EEG (QEEG). Studies examining waking EEG and sensory evoked potentials before and after single doses and chronic intake of standard neuroleptics have been

accomplished in schizophrenic patients. QEEG changes have been reported in specific EEG frequency bands with significant associations with plasma neuroleptic levels and indications of therapeutic response.(38,39) QEEG investigations with atypical agents are in progress. Small et al.(40) reported significant negative rank order correlations between D2 receptor affinities and spectral energy in the theta band (4 to 8 Hertz (Hz)) with lowest amplitudes after 4-6 weeks of optimal therapeutic doses for haloperidol followed by risperidone, olanzapine, quetiapine, and clozapine. However these determinations were based upon animal data which are not directly applicable to humans. There were positive associations between the purported degree of histamine receptor binding of the four atypical neuroleptics with highest amplitudes in the fast beta-2 band (18-30 Hz) with quetiapine followed by olanzapine, clozapine, and risperidone.

Other CNS adverse effects include a range of impairments that can be encompassed under the rubric "behavioral toxicity". These reactions may be idiosyncratic or related to dose and timing. Atypical neuroleptics are particularly prone to induce or expose obsessive-compulsive features(41,42). This has not yet been reported with quetiapine but has been observed by the author. Receptor data suggest that withdrawal symptoms would be likely to occur with quetiapine. However abrupt withdrawal of quetiapine

with switchover to standard neuroleptics was associated with psychotic relapse in only 2 of 50 patients studied by Goldstein without associated physical problems(43). Higher than optimal dosages can be associated with increased agitation and other indications of psychotic worsening as well as other side effects. Sleep disturbances with either sedation or insomnia may accompany drug therapy but may also be features of underlying psychosis.

Endocrinological effects:

There were no significant elevations in serum prolactin in the pivotal trials described previously and in some instances quetiapine was associated with reduced levels from baseline. Prolactin levels were significantly higher with both chlorpromazine and haloperidol. There were no significant differences between quetiapine and placebo in either men or women. In the absence of hyperprolactinemia problems such as gynecomastia, menstrual irregularities, impotence, etc. would not be expected although most trial durations were not long enough to evaluate these issues. Likewise reproductive and neonatal difficulties have not been reported to date.

However weight gain was an adverse event experienced by two percent of quetiapine patients in the placebo controlled studies. Clinically significant weight gain, that is more than 7 percent

increase in body weight, was seen more with quetiapine than placebo - 24 percent compared with four percent in the Borison et al. study. Weight gain appeared to be dose related in the Small et al. and Arvanitis et al., trials ranging from five percent for placebo, fifteen percent for low dose and twenty-four percent with high dose quetiapine in the former. Likewise weight gain in the Arvanitis et al. study was proportional to dosage and exceeded amounts with haloperidol and placebo. Twenty-seven percent of quetiapine treated patients had significant weight gain compared with eighteen percent with chlorpromazine reported by Peuskens and Link.

Adverse effects of atypical antipsychotics upon glucose regulation have been recognized recently mostly with clozapine. Hägg et al.(44) compared clozapine patients with those on depot standard neuroleptics and found hyperglycemia in thirty-three percent with clozapine and nineteen percent with traditional antipsychotics ($p=.07$). Non-insulin-dependent diabetes mellitus or impaired glucose tolerance occurred in twenty-one percent of the clozapine patients versus 9.5 percent of those taking standard neuroleptics ($p=.06$). Likewise the incidence for clozapine was over three times the expected number of cases based on population surveys. New onset diabetes has also been reported with olanzapine(45). It appears that atypical neuroleptics may promote weight gain, insulin insensitivity and glucose intolerance by virtue of their antagonism of histamine and serotonin receptors. African-Americans are

particularly vulnerable to these effects and individuals with personal or family histories of diabetes mellitus or obesity. As clozapine, olanzapine and quetiapine cause the most weight gain, these drugs may be most likely to induce diabetes. Case reports with quetiapine have not appeared so far.

Quetiapine was associated with small reductions in mean total T4 and occasionally T3 but these were not associated with concomitant elevations of TSH or any indications of clinical hypothyroidism. Maximal reductions occurred in the first two to four weeks of treatment with no further decline with continued intake. In nearly all instances discontinuation of quetiapine was followed with prompt reversal of effects on both total and free thyroxine.

Cardiovascular, gastrointestinal, and hematologic abnormalities:

Quetiapine exerts some cardiovascular effects such as orthostatic hypotension and dizziness. These usually occur during the initial period of dosage titration and seldom require discontinuation. EKG recordings showed little change in QTc intervals and there was no relationship between plasma levels of quetiapine and the QTc changes. Quetiapine appears to have minimal proarrhythmic activity. However in both reported cases of overdosage there was sustained sinus tachycardia persisting up to 48 hours. A further disclaimer should be added that experience has yet to be obtained

in patients with preexisting heart disease and EKG abnormalities. The major gastrointestinal effects of quetiapine are mild transient, reversible and asymptomatic elevations in serum transaminase (ALT, AST) or gamma-glutamyl/transferase levels. These abnormalities did not exceed five times the upper limits of the normal range for the laboratory assay and were generally reversible despite continued treatment. Constipation was endorsed as a problem in fewer than ten percent of patients, similar to the incidence with placebo. However weight gain was a significant issue as discussed previously.

Hematologic abnormalities are of particular concern in the light of the experience with clozapine. No cases of granulocytopenia have been noted to date nor any deaths that could have been the result of undetected agranulocytosis. Although there appear to be no hematologic problems with quetiapine it should be recognized that patients with preexisting abnormalities or individuals predisposed to these complications were excluded from the systematic trials. Moreover combinations of quetiapine with other agents have yet to be studied.

Ophthalmologic effects:

Quetiapine was associated with the development of cataracts in dogs that received quetiapine at four times the maximum recommended

human dose for six to twelve months. No evidence of cataracts appeared in a comparable study of monkeys at even higher doses and none have been observed in humans. Nevertheless labeling for now recommends that periodic slit-lamp examinations be done before quetiapine treatment and at six month intervals thereafter. Complicating this situation is the high incidence of cataracts in patients with schizophrenia as well as longitudinal changes that occur with advancing chronological age(46).

Pharmacokinetics and Drug Interactions:

The plasma half-life of quetiapine is 6 to 8 hours but the half-life of receptor occupancy may be longer as mentioned earlier. Gefvert et al.(47) compared plasma half-life and D2 and 5-HT2 receptor occupancies finding that the latter declined more slowly than plasma levels, particularly 5-HT2. Fleischhacker et al. (48) compared twice and three times daily dosage regimens of quetiapine and observed a few advantages for twice daily dosing, results supported by PET studies of receptor occupancy.

Quetiapine is rapidly absorbed after oral administration with peak blood levels in 1 to 1-1/2 hours. It appears to be widely distributed in tissues and extensively metabolized in the liver with only a small amount of the parent compound excreted in the urine. The major metabolic pathway involves sulphoxidation by

cytochrome P450 3A4 although CYP 2D6 may also play a role(49). Consequently elevated plasma levels of quetiapine can be anticipated with co-administration of enzyme inhibiting drugs such as ketoconazole, erythromycin, nefazodone, fluvoxamine, and some other antidepressants. 3A4 enzyme inducers such as phenytoin and to a lesser extent thioridazine can increase both clearance and dosage requirements but quetiapine levels will likely rise when the inducer is stopped.

Therapeutic Potential:

Results from randomized, double-blind clinical trials conducted thus far indicate that a wide dosage range of quetiapine is well tolerated and effective in the treatment of positive and negative symptoms of schizophrenic exacerbations. Preclinical and clinical data support its status as an atypical antipsychotic drug with few Parkinsonian, extrapyramidal or other neurological side effects. Although comparative data are not yet available quetiapine may offer the widest dosage range with fewest neurological side effects of all the marketed atypicals. Lack of effects on prolactin predicts few if any sexual dysfunctions and other endocrinological side effects that impinge upon patient compliance. The absence of cardiovascular effects is another desirable feature that may reduce or eliminate the need for dosage titration, although this must be

investigated further. Likewise its weak anticholinergic activity offers potential advantages for patients with cognitive impairments. However weight gain is a significant adverse effect that may limit acceptance as will the required twice daily oral dosing schedule and the ophthalmologic examinations.

Quetiapine's eventual place relative to the other atypical neuroleptics remains to be established. Studies of these applications are appearing rapidly at national and international scientific meetings. Clinical trials in progress include studies of nursing home residents with Alzheimer's dementia and psychosis, studies of psychotic adolescent patients, further investigators of Parkinsonism and combinations of quetiapine and carbamazepine(50).

Data have been already collected from industry supported multicenter trials of treatment refractory schizophrenic patients which should be analyzed and reported in the near future. In this regard an abstract from Japan on refractory patients appeared in a recent program(51). Numerous other investigations are in progress which should soon establish the place of quetiapine in the therapeutic armamentarium.

Figure 1. Structural formula.

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ADDITIONS

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EXHIBIT 9

Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
+ Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the hadoperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 – 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (± 9.6) kg at week 104, 5.7 (± 10.9) kg at week 156, and 6.7 to 7.3 (± 9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 – 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 – 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 – 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 – 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated Hba1C (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as...quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 – 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 – 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Sernyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 – 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 – 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members, NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fac, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools...across parameters / measures...across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; $P<0.001$). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; $P<0.001$ and 0.53; $P<0.001$, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.

Donna K. Arnett

Donna K. Arnett, Ph.D., M.S.P.H.

Id : i.m.c22c37e56740fa1f408e63eba6fa447b
CN : S339-E01167234
Date : Tuesday, December 4, 2007 1:39:49 PM GMT
From : "Rak, Ihor W" <ihor.rak@astrazeneca.com>
To : "Goldstein, Jeffrey M" <jeffrey.goldstein@astrazeneca.com>
Subject : Re: information
Custodians : Goldstein, Jeffrey

From: Rak, Ihor W

Sent: Tuesday, December 04, 2007 1:40 PM

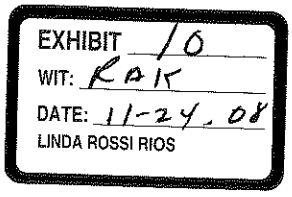
To: Goldstein, Jeffrey M

Subject: Re: information

Jeff

Thanks for reaching out to me - I will look into this and we should discuss. When is your must decide date so I know how much time I have?

Ihor



Sent from my BlackBerry Wireless Handheld

----- Original Message -----

From: Goldstein, Jeffrey M

To: Rak, Ihor W

Sent: Mon Dec 03 19:49:04 2007

Subject: information

Dear Ihor,

I need to make a very difficult decision over the next few weeks and I wanted to reach out to you for advice. A few weeks ago we chatted briefly and I told you that I was anticipating a promotion to Senior Director but things have not progressed as fast as I had hoped, and the recent reorganization may have removed this from peoples radar screens. I was counting on this promotion to bring me to Band 7 and allow the cap on my salary to be removed because over the past three years I have not received a raise. This was because my salary in relation to the MRP for Band 6 is above the accepted limits. Although I have received a lump sum each year in lieu of a raise, it has not figured into my bonus or pension. You can imagine how frustrated I am in view of my excellent performance reviews. I recently did some calculations and if I were to retire at the end of this year the company would have to add 6 weeks of banked vacation plus an additional week that I was allowed to carryover into 2008. That would make 2007 my best grossing year (assuming my bonus is on par with previous years) and my pension would increase. That is a very attractive option for me. However, I am hesitant to act on this urge as I feel I still have a lot to offer this company and my passion for Seroquel has far from ended. And, there is a lot going on with Seroquel under the pretense of science that needs serious review. So to be very frank with you and the reason for this email is to ask the following questions - am I being considered for promotion to Senior Director, when will this likely happen, and will my salary increase appropriately? Sorry if I am putting you in a difficult situation but I need to make a decision very soon and you are the only one who can provide me with the answers to those questions.

I will be traveling this week to Budapest to make 2 Seroquel presentations at IFMAD, and then on vacation for the rest of the year although I am giving up several vacation days to handle urgent matters not the least of which is to continue to meet with the attorneys who are preparing me for my January deposition. I regularly check my email when home (a habit I cannot seem to break) so except for my time in Budapest I will look for a response from you. I would also welcome some time with you to discuss this further if you think that would be best and would happily give up some vacation time to meet at your convenience.

I truly hope that AZ will reward and recognize me with a promotion but more importantly give me the opportunity to take on a more senior leadership role. I truly believe our group needs a senior person to step in and question the science being presented at several levels. I look forward to hearing back from you.

Sincerely,

Jeff

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalcyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Patterson
Exhibit No. 8
6.11.08 C. PERKS

22

[illegible] age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like?
For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Shold we get together to chat?

Thanks
Lisa

EXHIBIT 7

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	:CASE NO. :6:06-md-01769-ACC-DAB
MDL Docket No. 1769:	

- - -

December 20, 2007
CONFIDENTIAL

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Oral deposition of WAYNE MACFADDEN, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania, beginning at 9:01 a.m., on the above date, before Ann Marie Mitchell, a Federally Approved Certified Realtime Reporter, Registered Diplomate Reporter and Notary Public for the Commonwealth of Pennsylvania.

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GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
1650 Market Street
Philadelphia, Pennsylvania 19103
877.370.3377

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MR. FRITCH: David Fritch with Dechert.
MR. LeGOWER: Donald LeGower with Dechert on behalf of AstraZeneca and the witness.
MR. McCONNELL: Stephen McConnell with Dechert LLP representing defendant AstraZeneca and the witness, Dr. Wayne Macfadden.

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EXAMINATION

- - -

BY MR. ALLEN:

Q. Good morning.
A. Hello.
Q. Can you tell the jury your name, please, sir?
A. My name is Wayne Macfadden.
Q. You're a medical doctor?
A. Yes.
Q. Can you tell the jury how you're employed?
A. Currently?

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Q. Yes, sir.
A. I'm employed at Johnson & Johnson.
Q. Johnson & Johnson Pharmaceuticals?
A. Yes.
Q. Is that the distributor of Risperdal?
A. The Johnson & Johnson family of companies manufactures risperidone, yes.
Q. Risperidone is the generic name of Risperdal, the brand name?
A. Yes.
Q. Tell the jury what Risperdal is.
A. Risperdal is a medication in the antipsychotic class. It's approved for the treatment of schizophrenia.
Q. Do you work on Risperdal?
A. I work on a formulation of risperidone.
Q. Tell the jury who your -- how long you've worked at Johnson &

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Johnson, Janssen.
A. Approximately one year.
Q. Can you give us the approximate start date at Janssen & Janssen? Or Johnson & Johnson, which Janssen -- let me ask this question.
Janssen is a division of Johnson & Johnson?
A. Janssen is one of the operating companies within Johnson & Johnson.
Q. How long -- how long have you -- you said that you worked there approximately a year.
Do you recall when you started?
A. I believe it was November of last year.
Q. November of 2006?
A. Yes.
Q. Just for the record, today is December 20, 2007. Correct?
A. Yes.
Q. Prior to the time that you

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worked at Johnson & Johnson -- let me ask this question. You said you worked at Johnson & Johnson.
Do you work for Janssen, the Janssen division?
A. My division is Ortho-McNeil Janssen Scientific Affairs.
Q. Okay. Prior to working at that pharmaceutical company, where did you work?
A. I was employed at AstraZeneca.
Q. When did you leave AstraZeneca?
A. It was the summer of 2006.
Q. What month?
A. It was August or September, I can't -- one of the two.
Q. Okay. So you had approximately two months off before you began to work at Janssen?
A. Yes.
Q. Okay. Were you terminated or fired from AstraZeneca, or did you

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just leave for better opportunities?
A. I resigned from AstraZeneca.
Q. Why did you -- let me ask this.
Was the resignation a voluntary resignation or a suggested resignation?
A. I chose to resign from AstraZeneca.
Q. And when did you make that decision?
A. Either August or September 2006.
Q. Did you give two weeks notice at the time of resignation, or did you resign and then leave on the same day?
A. I resigned and left on the same day.
Q. Thank you, sir.
Dr. Macfadden, you understand you've been sworn to tell the truth, the whole truth and nothing but the truth.

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Do you understand that?
A. I do.
Q. Do you understand that the oath is a serious matter?
A. Yes.
Q. And the oath says the truth and the whole truth.
Do you understand there's a distinction between the truth and the truth and the whole truth? Do you understand there's a distinction?
MR. McCONNELL: Objection to form.
THE WITNESS: Perhaps you should explain.
BY MR. ALLEN:
Q. Well, let me ask this.
What does it mean to you when you've been sworn in to tell the truth and the whole truth? What does that mean to you as a person who took the oath in this case?
MR. McCONNELL: Objection to form.

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THE WITNESS: I swore to tell the truth.
BY MR. ALLEN:
Q. Okay. Have you ever given a deposition or any sworn testimony before?
A. Yes.
Q. And when did that occur?
A. I don't recall the exact date.
Q. How many times have you given a deposition or sworn testimony before?
A. I've given a deposition once.
Q. Prior to today. Correct?
A. Yes.
Q. Other than that one deposition prior to today, have you given any other sworn testimony before?
A. I have, yes.
Q. Where else? You said you gave a deposition?
A. Yes.
Q. What else?

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A. It was a testimony in a case where I was called in as an expert witness.
Q. Any other testimony, sworn testimony, besides the deposition and the testimony in a case?
A. No, not that I recall.
There was one or two times that -- I think it was twice, that I gave a -- testimony as an expert.
Q. In a courtroom?
A. Yes.
Q. Okay. Anything else?
A. No, I don't recall.
Q. Okay. Here's what I've written down based upon your testimony.
You believe you've given a deposition once before, you don't recall the date, and you believe you've given testimony as an expert in two court cases; is that right?
MR. McCONNELL: Objection to form.
THE WITNESS: That's the

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What did you write?
A. It appears to say "52-week comparison in stabilized patients. 75, 300, 600, 12 Haldol. Primary time to WD," withdrawal.
Q. What does all of that mean?
A. It appears to imply a 52-week study in stabilized patients with 75, 300 and 600, and 12 milligrams Haldol.
Q. Did you learn about the weight gain data in -- of consistent weight gain to a medically significant degree when you were looking into study 15?
A. I don't recall being appraised of that, no.
Q. Remember you told me CAFE was one of the main ones you were in charge of, right?
A. I was the AstraZeneca physician assigned to participate in the study meetings that were conducted by the PIs.

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Q. That was a loser for -- CAFE internally at least when you took your notes, CAFE was a loser when compared with Zyprexa and Risperdal, right?
A. My recollection was that the endpoint was a noninferiority design. My recollection was that the various arms were indeed noninferior to each other.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'll tell you what. Help us out with, as opposed to your external communication, what your internal handwritten note says, read it aloud, please.
MR. MCCONNELL: Objection, form.
THE WITNESS: "Loss on PANSS plus versus OLZ" and RAS.
BY MR. ALLEN:
Q. Doesn't that mean Seroquel lost on the endpoints in the study when compared with Zyprexa and Risperdal?

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A. My recollection was that in trying to understand this, is that there may have been numerical difference between the three arms. However, my recollection was that the primary endpoint was achieved.
Q. Your note says Seroquel "loss," right?
A. Yes.
Q. I'm going to ask you a series of questions on that note about -- following your testimony about your handwritten note about Seroquel loss. I'm going to read them. And I just need your answer.
Dr. Macfadden, were there any clinical trials on Seroquel -- let me rephrase the question.
Dr. Macfadden, was there any clinical trial on Seroquel when it was compared with an active comparator, second generation antipsychotic where Seroquel was shown to be superior with statistical significance in efficacy as

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defined by the study's primary endpoint.
A. Excuse me. Could you read that one more time, please?
Q. Yes, sir. Was there any -- are you aware of any clinical -- let me rephrase it.
Are you aware of any AstraZeneca clinical trial on Seroquel comparing Seroquel to another second generation antipsychotic where Seroquel was shown to be superior with statistical significance on efficacy as efficacy was defined by the study's primary endpoint?
A. That's your question to me now? My recollection was that there was not a study in which there was a significantly -- significant advantage in efficacy for Seroquel compared to other atypicals to the best of my recollection.
Q. Thank you, sir.
This question.
Are you aware of any AstraZeneca clinical trial on Seroquel when compared with a first generation

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antipsychotic where Seroquel was shown to be superior to a degree of statistical significance on efficacy as defined by the study's primary endpoint?
A. To the best of my recollection, there was -- I can't recall a study in which Seroquel demonstrated statistically significantly superior efficacy compared to an atypical regarding schizophrenia.
Q. Yes, sir. And I didn't ask about atypical in my question. Now I'm not talking about first generation. You know the difference between first generation antipsychotics and atypical antipsychotics, do you not?
A. Yes.
Q. So, listen to my question. Are you aware of any AstraZeneca clinical trial on Seroquel where it was compared with a first generation antipsychotic where Seroquel was shown to be superior to a degree of statistical significance on efficacy as efficacy was defined by

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the study's primary endpoint?
A. Not to my recollection, no.
Q. Dr. Macfadden, are you aware of any clinical trial on Seroquel with any active comparator where Seroquel was shown to be superior in efficacy to a statistically significant degree on any endpoint?
A. Excuse me. The comparator was which?
Q. Any?
A. I can't immediately recall a trial which has significant superiority for Seroquel compared to another antipsychotic.
Q. Thank you.
Dr. Macfadden, are you aware of any AstraZeneca clinical trial on Seroquel with an active comparator where Seroquel was shown to be less efficacious to a degree of statistical significance?
A. I can't recall a trial with that result, if one existed.
Q. I'm going to write down

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"Can't recall" on that.
Dr. Macfadden, are you aware of any meta-analyses on Seroquel where Seroquel was compared with active comparators where Seroquel was shown to be superior to a statistical degree of significance with any other antipsychotics?
A. I don't recall a study in which Seroquel was shown to be significantly superior in a meta-analysis with other antipsychotics, if that was your question.
Q. Dr. Macfadden, are you aware of any meta-analyses on AstraZeneca clinical trials where Seroquel was compared with active competitors and Seroquel was shown to be less efficacious to a degree of statistical significance?
A. If a study like that existed, I don't recall the results.
Q. Dr. Macfadden, are you aware of any AstraZeneca clinical trial on Seroquel where it was compared with a

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placebo control group and Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance?
A. To the best of my recollection, there was a single arm on one of the early registration studies that was either comparable to -- may not have been statistically significant, but I can't provide more details than that.
Q. So, you're just aware of one study, and you're only vaguely aware of it where Seroquel was no more efficacious than a placebo? You're just aware of one?
A. In the treatment of schizophrenia?
Q. That wasn't my question.
A. To the best of my knowledge, that was the one study I have a vague recollection about in which one of the arms may not have been statistically significant compared to placebo in the treatment of schizophrenia.

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Q. You're vaguely aware of one schizophrenia study?
A. Yes.
Q. How about nonschizophrenia studies such as study 41?
Well, maybe -- 41 could have been a schizophrenia study. I don't remember. Was it? Was the study on sustained release? I can't remember what the patient population was. I can find out.
Let me just ask, are you familiar with study 41?
A. I don't have a recollection of what study that number pertains to or the results.
Q. Given your answer about whether there's any clinical trial on Seroquel compared with a placebo controlled group where Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance, when you gave your answer, you were not aware of study 41?

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A. I don't recall the design of study 41 or what the results were.
Q. Okay.
When giving your answer about any clinical trial on Seroquel compared with the placebo where Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance, did you know about study 100?
A. I believe I gave my answer regarding schizophrenia, and I believe study 100 had something to do with bipolar disorder.
Q. In that study, 100, Seroquel was shown to be no more efficacious than an inert placebo, true?
A. I can't recall the specifics. However, there may have been a study in which Seroquel or placebo was added on to another medication.
Q. It was an adjunct study, Doctor. It was an adjunct mania study, as was study 99. When you gave the

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answer to the question about Seroquel being no more efficacious than a placebo, were you aware of studies 104 and 105?
A. I'd like to go back to the previous question. If it is an add-on study, it's not really a comparison of the second drug versus placebo since medications are already being taken.
Q. We'll debate that with somebody else, but let's make sure we're really clear because I do know about study 100. And what you did is you at AstraZeneca in the clinical trial gave some patients a combination of placebo and lithium and a medication that starts with a D, I can't pronounce it, divalproex. How do you pronounce that medication? You know what I'm talking about?
A. I think that's divalproex.
Q. Study 99, and I'm bad with divalproex, and I will probably butcher the name, I can't get it and I just studied it, and I just won't do it right.

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But study 100 combined a placebo with lithium or a placebo with divalproex versus Seroquel with lithium and Seroquel with divalproex, right?
MR. MCCONNELL: Objection to form.
THE WITNESS: That's my recollection of the general design, yes.
BY MR. ALLEN:
Q. Yes. Then when we compared the patients who were on placebo and lithium and placebo -- excuse me.
When we compared the patients who were on placebo and lithium with the patients who were on Seroquel and lithium in the primary endpoint, Seroquel was no more efficacious than the placebo arm, right?
A. No more effective than lithium alone compared -- and adjunct to placebo.
Q. Right.
Now, I'm going to go back

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to the specific marketing point you're referring to. However, when efficacy or efficaciousness is discussed, it often implies a combination of efficacy and tolerability.

MR. ALLEN: Objection, nonresponsive, completely.

BY MR. ALLEN:

Q. Doctor, did your company ever go out and tell anybody anywhere at any time that Seroquel is more efficacious than another second generation antipsychotic?

A. I don't know.

Q. Based upon the clinical trial data that you are aware of, could AstraZeneca honestly and truthfully go out and tell anybody Seroquel is more efficacious than another second generation antipsychotic?

MR. MCCONNELL: Objection to form.

THE WITNESS: To the best of

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my knowledge, there were no studies which showed a statistically significant advantage for Seroquel over competitors.

BY MR. ALLEN:

Q. Therefore, if any AstraZeneca employee or representative ever told anybody that our product, Seroquel, is superior on efficacy to another second generation antipsychotic, that would be a lie, wouldn't it?

MR. MCCONNELL: Objection to form.

THE WITNESS: With my understanding of the studies, they would be incorrect with that, yes.

BY MR. ALLEN:

Q. That's a nice way of saying it. It would be incorrect for anybody from AstraZeneca to ever have represented that Seroquel is more efficacious than any other second generation antipsychotic, right?

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MR. MCCONNELL: Objection to form.

BY MR. ALLEN:

Q. It would be incorrect?

A. As I say, I was not and I am not aware of any studies such as that that would show superior efficacy. Based on my recollection of the studies there, that would be incorrect, yes.

Q. That's a nice way of putting it. Another way of putting it, it would be false and untrue for AstraZeneca to have represented based upon the AstraZeneca clinical trial data that Seroquel was superior in efficacy to any other second generation antipsychotic, true?

MR. MCCONNELL: Objection to form.

THE WITNESS: Based on what I recall from the clinical trials, it would be incorrect to assert that Seroquel was more efficacious based on a lack of statistical

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superiority as I can recall it.

BY MR. ALLEN:

Q. It would not only be incorrect, it would be false, it would be untrue, and to put it bluntly, it would be a lie, true?

MR. MCCONNELL: Objection, form.

THE WITNESS: It would be incorrect. I can't speak about your other characterizations.

BY MR. ALLEN:

Q. Not only would it be untrue to say that Seroquel was more efficacious than a second generation antipsychotic, it would be untrue to say that Seroquel was more efficacious than a first generation antipsychotic, true?

A. It depends how the word "efficacious" is used. If it pertains to combinations of efficacy and safety, it is different than just efficacy alone.

Q. I'm talking about efficacy alone, Doctor. It would be untrue and

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wrong for AstraZeneca to represent that Seroquel was more efficacious than any first generation antipsychotic, true?

MR. MCCONNELL: Objection to form. Objection to the extent it calls for a legal conclusion.

THE WITNESS: To the best of my recollection, as I stated, there was no clinical trial in which Seroquel demonstrated statistically significant superiority over a typical antipsychotic, thus, to the best of my recollection, that would be false.

BY MR. ALLEN:

Q. Thank you.

And when you said "a typical," in that sentence, you were using "a" and "typical" as two separate words, right?

A. Yes.

Q. Now, when making a risk/benefit analysis, one must look at

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both efficacy and safety, true?

A. If a clinician is deciding on a medication, presumably they look at both safety and efficacy, yes.

MR. ALLEN: What's my next Exhibit Number? 39?

THE COURT REPORTER: Yes.

- - -

(Whereupon, Deposition Exhibit Macfadden 39, Handwritten document (1 page), was marked for identification.)

- - -

BY MR. ALLEN:

Q. Doctor, you have to look at the screen for 39 because you and I are going to create this together. You have the screen, you can see the exhibit?

A. Yes.

Q. The SQ on the left-hand column, we're going to have that stand for Seroquel. That's a common abbreviation in your company for Seroquel, is it not?

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A. I think SQL was more common, but, yes.

Q. You know what, SQL, that's Seroquel, right?

A. Yes.

Q. All others, we're going to put "all other antipsychotics." I'm a real bad speller, by the way.

Now, you've told us in regard to efficacy, which I'm going to put over here in the left hand -- you've given us your answer in regard to efficacy, and there was no superiority for Seroquel in the data that you're aware of, true?

A. There was no statistically significant superiority regarding efficacy endpoints to the best of my knowledge that I can recall.

Q. And so I would like to add "statistical." By the way, in the scientific field there at AstraZeneca, that's what's important, isn't it, statistical significance?

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A. Statistical significance and clinical significance are both important.

Q. You're a pharmaceutical physician. That's how you described yourself yesterday. Do you remember that?

A. I described myself as a physician being employed by a pharmaceutical company, therefore, a pharmaceutical physician, yes.

Q. I didn't use the term. Do you recall in an answer to my question, you volunteered that you said I am a pharmaceutical physician? Do you recall that?

MR. MCCONNELL: Objection to form.

THE WITNESS: Yes.

BY MR. ALLEN:

Q. In fact, I remember I asked you something, and you said, well, Mr. Allen, that was before I became a pharmaceutical physician. And I asked you when you became a pharmaceutical

Clinical Study

The weight profile of SEROQUEL over the long term

Authors: Brecher M, Rak IW, Melvin K, et al.

Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

Journal: *International Journal of Psychiatry in Clinical Practice* 2000;4:287-291.

Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - —178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - —Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - —BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

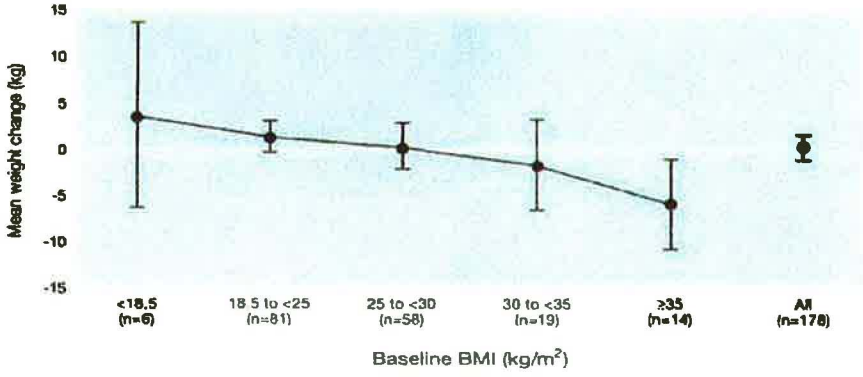
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*Last recorded weight measurement

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



 International Journal of Psychiatry in Clinical Practice 2000 Volume 4 Pages 287–291

The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

M BRECHER,[1] IW RAK,[1] K MELVIN[2] AND AM JONES[2]

AstraZeneca, [1]Wilmington, DE, USA and [2]Alderley Park, Macclesfield, Cheshire, UK

Correspondence Address
Dr Martin Brecher, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE, USA
Tel: +1 (302) 886 2634
Email: martin.brecher@astrazeneca.com

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INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 *kg/m*^{2}*) and severely obese patients (BMI* ≥ 35 *kg/m*^{2}*).*

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[1] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
<50 kg	5
50–70 kg	171
71–90 kg	164
>90 kg	59

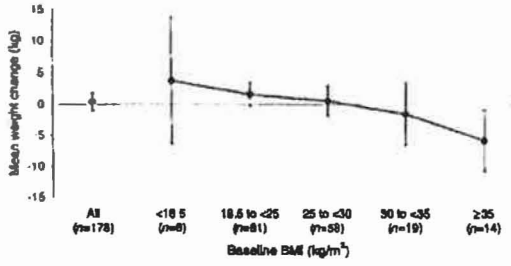


Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg

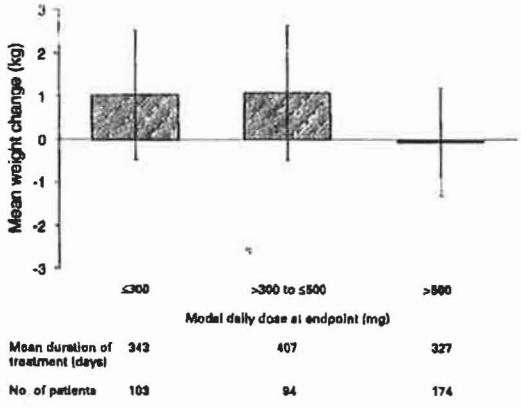


Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m^2)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5<25	81	468	539	1.6
≥25<30	58	466	607	0.53
≥30<35	19	514	551	−1.53
≥35	14	483	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,16,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m^2), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.

Unknown

From: Aked Dominic DM
Sent: Thursday, October 26, 2000 9:30 PM
To: Rak Ihor IW
Cc: O'Brien Shawn SP; Shadwell Pamela PG; Holdsworth Debbie D; Jones Martin AM - PHMS
Subject: RE: Data for weight neutral slide

Hi Ihor

Many thanks for this important feedback.

I agree we need to be able to tell a convincing story to our internal and external customers. I'm sure we can do this.

- Re US PI: From what I can see any mention of weight gain in the US PI relates to short-term studies. We may be able to make a clear distinction between this clinical situation and long-term treatment (that is, acutely psychotic relapse versus long-term maintenance). Presumably the latter is what is important clinically given that patients receive long-term treatment.

A promotional claim ***'Seroquel is weight neutral during long-term treatment*** should help to make this distinction.

- There may be a rationale to explain why acutely psychotic patients may gain weight in the short term, following effective therapy. The relief of negative symptoms, apathy etc, disorganised thinking, may result in return to normal activities like having regular meals.

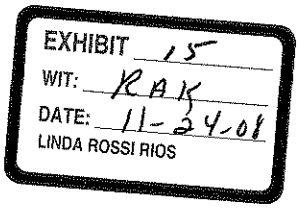
There are useful indicators in the patient satisfaction study to support the view that effective long term therapy with Seroquel helps to normalise eating.

Benefits noticed in last 6 mo by patients on Seroquel
55% patients prepare and cook meals
64% go shopping for food/personalitems
73% eat more normally
Page 25 Figure 4C Clear Perspectives Vol 2 issue 3

One additional comment (where there's a ying there's a yang): if we look at incidence of patients gaining >7% baseline weight, we should also consider looking at patients losing >7% baseline weight, or what would be considered a clinically significant weight loss.

Kind regards

Dom

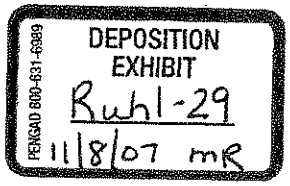


From: Rak Ihor IW
Sent: 25 October 2000 02:16
To: 'Rob Kite'; Holdsworth Debbie D; Jones Martin AM - PHMS
Cc: Shadwell Pamela PG; Ashworth Phillip P; Aked Dominic DM; Gavin Jim JP; O'Brien Shawn SP
Subject: RE: Data for weight neutral slide

All

I had the pleasure of presenting 5 weight slides (from the International Speaker's Training meeting) to the US SEROQUEL Product Team.

The titles of the 5 slides were; SEROQUEL-minimal effect on weight long term; SEROQUEL- neutral effect on weight at all doses; 3 slides-- Long-term SEROQUEL monotherapy has neutral effect on weight (1 with confidence intervals, another n=112 of 53 weeks exposure and longer shifts in BMI category, and another shifts in BMI category in obese/severely obese patients).



53

They had some very good suggestions based on their having to deal with the US label which states that SEROQUEL causes dose related weight gain (NDA dataset).

1. Best to tell a story. Data from clinical trials showed this, but limitations are these. hence another dataset analysed

2. using different datasets raises suspicions if not adequately explained and justified.

3. when selecting a cohort of patients who were treated for 26 or 53 weeks minimum, suspicions are immediately raised about the patients "censored": what was their mean weight change. For both cohorts of patients (those displayed and those censored) how many experienced adverse events (weight gain >7% of body weight), how any discontinued from the OLE due to weight gain, etc

4. BMI shifts not quickly understood; patients can not shift fromtheseverely obese BMI category (already mentioned)

Certainly, the more of these comments that we examine and address, the more confidence we will have in our weight neutral message.

Ihor

From: Jones Martin AM - PHMS
Sent: Friday, October 20, 2000 10:25 AM
To: 'Rob Kite'; Holdsworth Debbie D
Cc: Shadwell Pamela PG; Ashworth Phillip P; Rak Ihor IW; Aked Dominic DM; Gavin Jim JP
Subject: RE: Data for weight neutral slide
Importance: High

Rob

Please find attached a word document containing the data that you need. There are 40 pages in totally. The first 20 refer to all doses, the last 20 to data from within the 150-750 mg dose range.

In yesterday's Communication Planning Team meeting, it was decided to focus on the all dose cohort, for which we have 178 schizophrenic patients, with weight data beyond day 182, with BMI data. This data is slightly different to that previously included in my slide.

The summary data for this cohort starts on page 6, with :

	N	Mean	LCL	UCL	Median	Min	Max	Std Err	t Prob>|t|	TINV
All	178	0.412	-0.910	1.743	-0.450	-27.00	27.000	0.991	0.674	0.612	0.728	1.973

From this you should be able to get all the required data. The following page contains mean dose data for the entire cohort.

The next dozen or so pages divide these 178 patients into demographic sub-groups i.e. baseline BMI, gender, age group, race, mean dose group (interesting ?). All the tables should contain data for 178 patients !

The analyses are then repeated for the 150-750 mg group.

Hope this helps.

I am away on holiday next week, but Pamela, or Phill Ashworth may be able to help you with any queries.

Regards

AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

Date July 2008

SEROQUEL™ (quetiapine fumarate)
Clinical Overview on Weight Gain in pediatric patients

Authors:

Leigh Jefferies M.D.
Global Safety Physician
Patient Safety, Wilmington, DE

Eva S.K. Alam, M.S., Pharm.D., RPh
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

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1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL is to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

1.2 Proposed label change

The following text will be added to Section 4.8 *Undesirable effects* of the SEROQUEL CDS under a subheading of *Children and adolescents.*

Children and adolescents

The same ADRs described above for adults apply to children and adolescents. The following table summarizes ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained $\geq$ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Since clinical trials in pediatric patients have been conducted with SEROQUEL and not SEROQUEL XR this change applies only to the SEROQUEL CDS.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

5.1.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer-term open-label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a brief description of these three trials.

- D1441C00112: a 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D1441C00149: a 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D1441C00150: a 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.2 Acute placebo-controlled data

5.1.2.1 D144C00112

Mean increase in body weight

In study D144C00112, mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine-treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (23.21% in the 400 mg/day and 18.18% in the 800 mg/day) had ≥7% weight gain at Day 42 compared to the placebo-treated patients (6.82%) (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.2)	10 (18.2)	3 (6.8)

5.1.2.2 D144C00149

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine-treated group, 1.7 kg in the 600 mg quetiapine-treated group and 0.4 kg in the placebo group. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (see Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (14.47% in the 400 mg/day and 9.88% in the 600 mg/day) had ≥7% weight gain at Day 21 compared to placebo-treated patients (0%) (see Table 4).

Table 4 D144C00149: Patients with ≥7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.5)	8 (9.9)	0 (0)

5.1.3 Longer-term open-label pediatric data

5.1.3.1 D1441C00150

Study D1441C00150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study D144C00112) and in children and adolescents with bipolar I disorder (continuing from Study D144C00149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania. Sixty-three percent of patients (241) completed 26 weeks of therapy with quetiapine.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 5.

Table 5 **Study D1441C00150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.3	113	64.8	19.2	175	65.7	18.2
Change from 112 DB BSLN	62	4.1	8.5	113	4.8	10.8	175	4.6	10.0
Change from 150 OL Baseline	62	4.3	6.9	113	2.8	10.1	175	3.3	9.1
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.9	136	64.5	18.4	200	65.8	19.6
Change from 149 DB BSLN	64	5.8	6.4	136	5.1	5.7	200	5.3	5.9
Change from 150 OL Baseline	64	5.5	5.8	135	3.2	4.8	199	4.0	5.2
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.3	249	64.7	18.7	375	65.7	19.0
Change from DB BSLN	126	5.0	7.50	249	5.0	8.3	375	5.0	8.1
Change from 150 OL Baseline	126	4.9	6.4	248	3.0	7.6	374	3.7	7.3

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial D1441C00150, the mean change in weight from OL baseline was 4.4 kg.

Patients with ≥7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 6).

Table 6 **Study D1441C00150: Patients with ≥ 7% weight gain (Summary safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥7% increase in weight from OL baseline.

5.1.4 Additional analysis of Pediatric data

5.1.4.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI), since with BMI, the weight is adjusted for height (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z-score taking into consideration the age and gender of the subject. Z-scores are able to show how different a child's weight or BMI is from the average children of the same height (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z-score of 0.5 over any duration of time (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study D1441C00150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group (see Table 7).

Table 7 **Study D1441C00150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.2	113	**-0.1**	1.4	175	**0.0**	1.3
Week 26	41	0.4	1.1	86	0.1	1.22	127	0.2	1.2
Final Visit	62	**0.5**	1.0	113	**0.2**	1.3	175	**0.3**	1.2
149 DB Baseline	67	**1.0**[a]	1.0	138	**0.9**[a]	1.1	205	**0.9**[a]	1.0
Week 26	37	1.2	1.0	77	1.2	1.0	114	1.2	1.0
Final Visit	63	**1.2**	1.0	135	**1.0**	1.0	198	**1.1**	1.0
DB Total Baseline	129	**0.6**	1.2	251	**0.4**	1.3	380	**0.5**	1.3
Week 26	78	0.8	1.1	163	0.6	1.2	241	0.7	1.2
Final Visit	125	**0.9**	1.0	248	**0.7**	1.2	373	**0.7**	1.2

[a] The mean BMI Z score at baseline is much higher for the 149 population

Table 8 below shows patients who had a ≥ 0.5 shift in BMI Z-score during trial D1441C00150 from both DB baseline and OL baseline and by indication. Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Table 8 **Patients with ≥ 0.5 shift in BMI Z score in Study D1441C00150 by indication**

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Patients with ≥0.5 shift in standardized BMI Z-score in Study D1441C00150 by age group

A similar percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (28% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (25% at EOT) from the DB baseline (see Table 9).

A higher percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (24% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (8.6% at EOT) from the OL baseline (see Table 9).

A similar percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (22% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (20.1% at EOT) from the DB baseline (see Table 9).

A higher percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (21% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (11.7% at EOT) from the OL baseline (see Table 9).

Table 9 **Patients with ≥0.5 shift in BMI Z score in Study D1441C00150 by age group***

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.1.4.2 Overall summary of pediatric clinical trial data

In trial D1441C00112, the mean increase in body weight was 2 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty-one percent of quetiapine patients and 7% of placebo patients had gained ≥7% of their body weight.

In trial D144C00149, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine patients and 0% of placebo patients had gained ≥7% of their body weight.

In trial D1441C00150, where 63% of patients (241/380) completed 26 weeks of therapy with quetiapine, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients had ≥7% increase in body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL Core Data Sheet and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL:

Name of the expert: Leigh Jefferies, MD
Global Safety Physician
Patient Safety

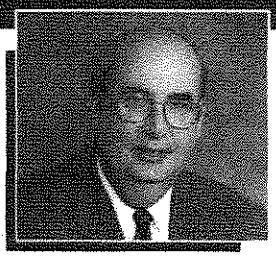
Signature:

Address:
1800 Concord Pike
Wilmington, DE 19850

Date:

According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.

Managing Weight Gain and Diabetes in Schizophrenia



A Patient Case Study

From the files of
Michael J. Reinstein, MD

Forest Foundation, Inc.
Clinical Research Department
Community Mental Health
Chicago, Illinois

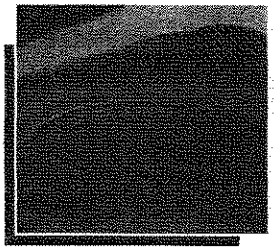


EXHIBIT 31
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

Patient Presentation

- A 49-year-old white male, unemployed, with a long history of psychiatric hospitalizations dating from age 25
- His various diagnoses include acute schizophrenic episode, paranoid schizophrenia, bipolar disorder, and schizoaffective disorder
- The patient also has a history of alcohol abuse

Past Medical/ Psychiatric History

- The patient was first hospitalized in 1976 with religious delusions, auditory hallucinations, and withdrawal
- He was subsequently hospitalized on several different occasions and followed on an outpatient basis after each discharge

Personal History

- There is no family history of psychiatric illness
- The patient was married with a son but has not had contact with either his wife or son for over 20 years
- He has not been gainfully employed for over 15 years
- He lives sporadically with either his mother or in homeless shelters

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. If its signs and symptoms appear, discontinuation should be considered.

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

Please see accompanying full prescribing information.

Mental/Physical Evaluation

- At presentation, the patient was alert and oriented to time, place, and person, maintained good eye contact, and was stable and in a cooperative mood
- Intelligence appeared to be within normal range
- He denied any hallucinations or ideas of reference
- No EPS, rigidity, or ataxia; no suicidal or homicidal ideations were expressed
- Judgment and reality contact were impaired, he appeared to have no insight, and he frequently laughed inappropriately in response to internal stimuli
- The patient answered questions only after considerable pauses—very briefly and in a low tone and volunteered no information whatsoever
- Physical evaluation revealed a patient overweight by approximately 10 lb

Treatment with SEROQUEL, like other antipsychotics, may result in somnolence, especially during initial dose titration.

Rationale for SEROQUEL Therapy

- Previous treatment with olanzapine 10 mg/day resulted in significant weight gain (10 lb) and subsequent development of type II diabetes (NIDDM)
- Accu-Chek™ was scheduled tid with sliding scale of Humulin® insulin

"This patient demonstrated some classic negative symptoms—blunted affect, emotional withdrawal, poor rapport, lack of spontaneity. Negative symptoms can often be very difficult to treat. We chose SEROQUEL for this patient because in our experience it provides excellent results with negative psychotic symptoms, and weight gain with SEROQUEL hasn't been an issue."

—Michael J. Reinstein, MD

SEROQUEL Dosing Regimen

- Olanzapine therapy was discontinued due to weight gain and the development of diabetes
- SEROQUEL was initiated at 150 mg/day for 1 week
- The SEROQUEL dose was then increased to 300 mg/day where it remains

Response to SEROQUEL

- The patient has shown a positive response to SEROQUEL, becoming more spontaneous, more interested in his surroundings, and has demonstrated improved interactions with others
- Blood glucose levels were brought under control, permitting the substitution of an oral hypoglycemic agent for insulin treatments
- Metabolic stability was maintained, allowing the patient to discontinue the hypoglycemic agent and return to a normal diet
- Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on olanzapine

"Our laboratory data revealed a normalization of serum glucose levels which is valid proof of improvement of diabetes and metabolic stabilization. His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also relieved that he no longer has to take daily insulin injections."

—Michael J. Reinstein, MD

Follow Up

- After 7 months, the patient remains well on SEROQUEL 300 mg/day
- The patient is currently taking part in a research study, where he perceives himself as a partner in a joint endeavor. He has achieved clinical improvement and a better quality of life
- He denies having any side effects and is considered competent to handle his own funds and supervised self-medication

"We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications."

—Michael J. Reinstein, MD

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported, and prescribing should be consistent with the need to minimize the risk.

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For a more normal life

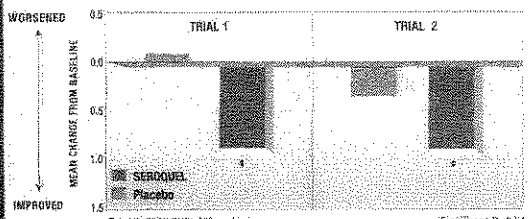
Please see accompanying full prescribing information.

The Strength to Control Both Positive and Negative Symptoms

Across well-controlled trials

Consistent Efficacy in the Treatment of Positive Symptoms[1,2]...

Mean Change in BPRS* Positive Symptom Cluster Scores (LOCF)[1,4†]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)

*Significant $P<0.01$

- **SEROQUEL significantly reduced positive symptom scores**

SEROQUEL was compared with placebo in the following well-controlled, 6-week, acute-phase, multicenter trials.

Trial 1: fixed doses of 75, 150, 300, 600, and 750 mg/day of SEROQUEL (n=255), placebo (n=51).

Trial 2: titrated doses up to 250 mg/day (low dose, n=94) and up to 750 mg/day (high dose, n=96) of SEROQUEL, placebo (n=96).

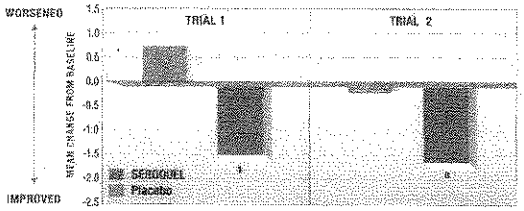
*BPRS: Brief Psychiatric Rating Scale is a clinical assessment tool that measures a combination of 18 individual positive, negative, and general symptom items. The BPRS positive symptom cluster score is the mean of 4 of the 18 individual symptom items for the clinical assessment of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

†LOCF: Last Observation Carried Forward.

Precautions listed in the label include orthostatic hypotension and the risk of cataract development.

...and Consistent Efficacy in the Treatment of Negative Symptoms[1,2]

Mean Change in SANS[5] Summary Scores (LOCF)[1,4]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)

*Significant $P<0.01$
†Significant $P=0.02$

- **SEROQUEL significantly reduced negative symptom scores**

[5]SANS: Modified Scale for the Assessment of Negative Symptoms is used to assess the negative symptoms associated with schizophrenia. The SANS summary score is a total of 5 global items: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention.

The most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).

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quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

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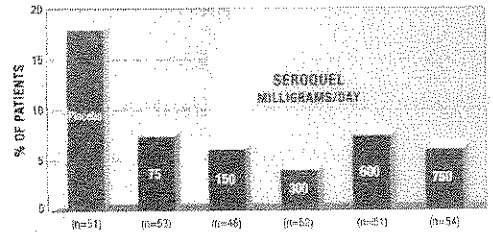
Please see accompanying full prescribing information.

Outstanding Overall Tolerability Across the Entire Dose Range

Across the entire dose range,* an EPS† profile no different from placebo

EPS Adverse Events by Dose[‡]

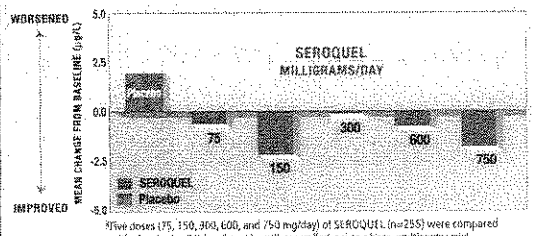


*In a 6-week, acute-phase, placebo-controlled trial.
†EPS: Extrapyramidal Symptoms were defined as dystonia, akathisia, and parkinsonism.
‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- No dose-related EPS were associated with treatment with SEROQUEL® (quetiapine fumarate)[5]

Across the entire dose range, plasma prolactin levels no different from placebo[5]

Mean Change in Plasma Prolactin Levels[‡]



‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- There were no statistically significant differences in plasma prolactin levels between any group taking SEROQUEL and the placebo group[1]

Minimal Weight Gain

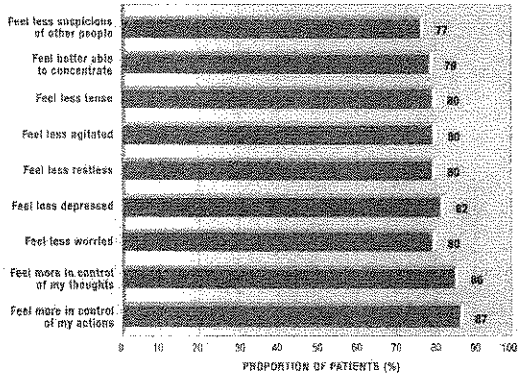
- In a recent open-label study, only 2.5% of patients treated with SEROQUEL (n=553) reported weight gain[6]

Patient Preferred

In a survey of patients (n=129) using SEROQUEL[7]

- 97% reported that they preferred SEROQUEL to previous medications
  - —Two reasons for preferring SEROQUEL were efficacy (29%) and tolerability (41%)[7]
- Benefits noticed in the last 6 months by patients using SEROQUEL

Efficacy-Related Benefits[7]



As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in all placebo-controlled clinical trials, weight gain was approximately 5 lb, which occurred mainly during the early weeks of treatment.[5]

Please see accompanying full prescribing information.

From: Hough Nick NW
Sent: 2/24/1999 8:30:56 AM
To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC; Tumas John JA
CC: Tugend Georgia GL
BCC:
Subject: RE: ECNP Abstract 'Weight gain & diabetes management'

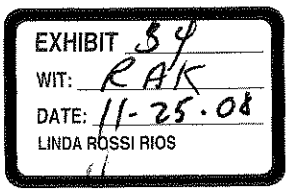
Hi John,

in principle it's the quality of the data, not the source that matters for promo claims etc. - providing, of course, that whatever the message is, that it is consistent with the totality of the data. We must not get too carried away with 'weight loss' when we know the rest of our data appears to point in the other direction, although a specific message related to the special nature of this particular finding might be possible. I need to see a full account of the data in order to be more certain at this stage. In some countries, however, a promotional claim can only be made if the data has been 'published' - usually this means a peer-reviewed journal. In the UK we can use 'data on file', but we must be prepared to supply it to anyone asking for substantiation, and if they don't like it they can complain to the relevant bodies. I guess there are different rules in the US? - as I understand it you can only make promotional claims based on the data/information in your actual labelling; I'd be interested to know more about this.

I hope this helps,

Nick

>----------
>From: Tumas John JA
>Sent: 24 February 1999 13:13
>To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC
>Cc: Tugend Georgia GL
>Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
>Actually, this abstract was submitted to APA, which will be the first time it is presented anywhere - that will be May 15 -20. I'm afraid that because it wasn't clear until the last minute if Dr. Reinstein was going to submit this, it never got on our abstract list.
>
>Bye the way, is it possible to make a claim from data that are not the result of a Zeneca trial?
>
> ----------
> From: Davies Diane DE - MMCC
> Sent: Wednesday, February 24, 1999 3:39 AM



> To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear Kevin
> If accepted, the abstract will be published at ECNP, which is September 21st 1999.
> To my knowledge this will be the first report of weight loss with seroquel - in this setting.
> kind regards
> Diane
> ----------
> From: Bill Kevin K
> Sent: 23 February 1999 22:52
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Is this the first mention of weight loss for SEROQUEL ?>
> If so when does it publish?
>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:20
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
> Subject: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear All
> Sorry for the previous e-mail which contained the abstract but no message.
> Please find attached an abstract for review. The abstract on the topic of 'management of weight gain and diabetes' is intended for submission to ECNP. The author, Dr Reinstein - a US investigator, has written this article which is reporting on his own study. This abstract has been deemed internationally important by the Communications Planning Team, therefore it is being subjected to international review. Should you have any comments on Dr Reinstein's abstract please forward them directly to John Tumas {you will see that there are some queries which need to be put to the author, these are italicised in the attachment}.
> Kind regards
> Judith Owens
> Ext: (2)8235
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:04

> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
>
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
>
>
>
>
>

Distinct advantages of a favorable weight profile

- Weight gain, commonly reported with some other antipsychotics, is associated with particular morbidities:
  —Type 2 diabetes, hypertension, coronary heart disease, cerebrovascular disease, certain cancers, and respiratory problems
- Minimal weight gain may reduce the likelihood that treatment with SEROQUEL will lead to diabetes and other morbidities associated with weight gain.
- Among patients taking antipsychotic medication, weight gain has been shown to cause more distress than other common adverse events

The most common adverse events associated with the use of SEROQUEL are dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The majority of adverse events are mild or moderate.[1]

In premarketing trials, the most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).[1]

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.[1]

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported.[1]

The safety and effectiveness of SEROQUEL in pediatric patients have not been established.[1]

As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in a placebo-controlled clinical trial, weight gain ranged from 0.9 kg to 2.6 kg.[2]

References: 1. SEROQUEL® (quetiapine fumarate) Prescribing Information, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. **2.** Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997;42:233-246.

Seroquel®
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

AstraZeneca

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437
Wilmington DE 19850-5437

7/01 201644

Please see Prescribing Information in pocket of this brochure.

www.SEROQUEL.com

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

REDACTED

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL

EXHIBIT 42
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

REDACTED

Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>

Judith Owens
Ext: 24164
11F34 Mereside

From: Eriksson, Hans A
Sent: Monday, July 07, 2008 3:53 PM
To: Rak, Ihor W; O'Dowd, Liza
Subject: FW: Updated Discussion document for the 09July08 Seroquel Peds SERM

Attachments: Weight SERM 09 July 2008.doc

Ihor and Liza,

Hot off the press, additional material for SERM.

Hans

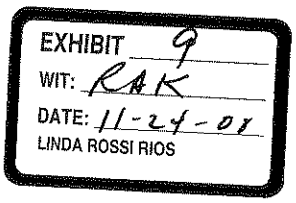
-----Original Message-----
From: Arnold, Karen
Sent: Monday, July 07, 2008 10:45 AM
To: Carey, Eileen; Dev, Vikram J; Arnold, Barry DC; Zander, Judith; Jefferies, Leigh; Leong, Ronald; Manning, Julia; Fors, Susanne (Seroquel); Boornazian, Lisa; Lee, Tara; Rolfe, Deborah; Warner, Linda (Safety); Delillio, Nina DH; Alam, Eva; Forsgren, Joachim; Spiers-Alston, Janet L; Gelman, Michele; Ni, Xiang; Eriksson, Hans A; Simpson, Brandon; Tyler, Robyn C; Åström, Mikael; Sherak, Nina; Walsh, Louisa M; Fullmer, Timothy S; Pathak, Sanjeev; Munro, Magna; Karlsson, Anders F; Patterson, Pat; Sullivan, Tim; Held, Peter; Stankowski, Jill; Nickless, Duncan M

Subject: Updated Discussion document for the 09July08 Seroquel Peds SERM

Dear all,

Additional data has been received for weight gain. An updated discussion document is attached. The new data is highlighted in yellow in the document.

Karen



AstraZeneca

Discussion Document

Drug name Quetiapine fumarate

Date *July 2008*

CONFIDENTIAL

Discussion Document

SEROQUEL/SEROQUEL XR AND WEIGHT GAIN

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

Author: Eva S. K. Alam, M.S., Pharm.D.
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

Leigh Jefferies, MD
Global Safety Physician
Patient Safety, Wilmington, DE

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APPENDICES

SUMMARY

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the current clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not actual weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 2.10, 3.00). The incidence rate in patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

1. INTRODUCTION

The purpose of this document is to review relevant information such as, clinical study data, received by AstraZeneca regarding the association of weight gain in pediatric patients with SEROQUEL treatment and to assess whether the Core Data Sheet for SEROQUEL requires amendment to reflect the company's current understanding of the subject.

2. BACKGROUND

2.1 SEROQUEL / SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research; and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt,Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and United Kingdom; written prescriptions from office based physicians) in which SEROQUEL/SEROQUEL XR is marketed.

2.2 Core Data Sheet for SEROQUEL and SEROQUEL XR

The AstraZeneca CDS presents the company position on the prescribing information for SEROQUEL and provides a reference for consistency of product information documents in individual markets.

The current SEROQUEL/SEROQUEL XR Core Data Sheets contain the following information regarding weight gain in Section 4.8:

"As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with SEROQUEL".

Frequency	System Organ Class	Event
Common (≥ 1% - < 10%)	Investigations	Weight Gain[3]

[3] Occurs predominantly during the early weeks of treatment.

The current frequency of common is based on AE reports and not actual weight data.

3. THE LITERATURE

Not reviewed for this topic.

4. PRE-CLINICAL DATA

Not reviewed for this topic.

5. CLINICAL STUDY DATA

5.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer term open label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a breif description of these three trials.

- D144C00112: A 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D144C00149: A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D144C00150: A 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.1 Acute placebo-controlled data

5.1.1.1 D144C00112

Adverse event data

Adverse events of weight increased were reported for three patients (4.12%) in the 400 mg/day mg/day quetiapine group, two patients (2.70 %) in the 800 mg/day quetiapine group, and two patients (2.66 %) in the placebo group. All adverse events of weight increased were judged related to the study medication by the investigator, and no adverse event of weight increased led to discontinuation of study treatment.

Mean increase in body weight

In study 112 mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥ 7% weight gain

A higher percentage of quetiapine treated patients (23.21 % in the 400 mg/day and 18.18 % in the 800 mg/day) had ≥ 7% weight gain at Day 42 compared to the placebo treated patients (6.82 %). (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.21)	10 (18.18)	3 (6.82)

5.1.1.2 D144C00149

Adverse event data

Adverse events of weight increased were reported for six patients (6.32 %) in the 400 mg/day quetiapine group, six patients (6.12 %) in the 600 mg/day quetiapine group, and none in the

placebo group. All adverse events of weight increased were judged related to study medication by the investigator and no adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine treated group, 1.7 kg in the 600 mg quetiapine treated group and 0.4 kg in placebo. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (See Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥ 7 % weight gain

A higher percentage of quetiapine treated patients (14.47 % in the 400 mg/day and 9.88 % in the 600 mg/day) had ≥ 7% weight gain at Day 21 compared to placebo treated patients (0 %). (See Table 4).

Table 4 D144C00149: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.47)	8 (9.88)	0 (0)

5.1.1.3 Pooled Data (Trials 112 and 149)

Adverse events of weight increase in pediatric studies D1441C00149 and D1441C0112 (pooled data)

In the pooled data, from the two acute placebo-controlled clinical trials (study 112 and study 149) with quetiapine in pediatric patients the incidence of reports of weight increased was 5.0 % in the quetiapine group and 1.2 % in the placebo group. The relative risk estimate (quetiapine vs placebo) was 4.13 (95% confidence interval: 0.96, 17.54). When adjusted for duration of exposure the incidence density for quetiapine was 64.8 per 100 patient years and 15.6 per 100 patient years for placebo. The relative incidence density was 4.17 (95% CI: 0.96, 18.03). (See Table 5).

Table 5 Number of patients with adverse events in pediatric studies D1441C00149 and D1441C00112

MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Relative risk QTP vs Pla	95%CI Lower	Upper	Incidence density[d]	Relative incidence density QTP vs Pla	95%CI Lower	Upper
Weight increased	QTP	17 (0)	340	26.2 (27.0)	5.0 (0.0)	4.13	0.96	17.64	64.8 (0.0)	4.17	0.96	18.03
	Pla	2 (0)	165	12.9 (13.0)	1.2 (0.0)				15.6 (0.0)			

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, cencored at first event.
[c] 100xtotal number of patients with event/total number of patients.
[d] 100xtotal number of patients with event/total patient-years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse ecent within the adverse event group, the number does not necessarily equal the sum of the numbers below.

Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Studies included: D1441C00149 and D1441C00112.
Derived from: Pgm: Reg-Def\Pediatric Apr08\...\AE_pla_ctrl. Data version: V15. User: Å Hellqvist. 07MAY08 14:20.

Patients with ≥ 7% weight gain by BMI (pooled data)

A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the majority of the different BMI categories (30.8 % vs. 9.5 % in the 0-<18.5; 18.6 % vs. 2.2 % in the 18.5 - <25; 5.2 % vs. 0% in the 25 - <30). A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group ≤ 12 year old in the majority of the different BMI categories. (23.8% vs. 0 % in the 0-<18.5, 16.3 % vs. 0 % in 18.5 - <25). Similarly, a higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group 13-18 year old in the majority of the different BMI categories (34.1 % vs.14.3 % in the 0-<18.5, 19.4 vs. 2.8 % in 18.5 - <25). (See Table 6).

Table 6 Patients with ≥ 7% weight gain by BMI in pediatric studies D144C00149 and D144C00112 (pooled data)

Weight Cut-offs	BMI group	PLA	All QTP	PLA ≤ 12	All QTP ≤ 12	PLA 13-18	All QTP 13-18
≥ 7 % increase at any visit		N n (%)	N n (%)	N n (%)	N n (%)	N n (%)	N n (%)
	0-<18.5	21 2 (9.5)	65 20 (30.8)	7 0 (0)	21 5 (23.8)	14 2 (14.3)	44 15 (34.1)
	18.5 - < 25	89 2 (2.2)	177 33 (18.6)	17 0 (0)	43 7 (16.3)	72 2 (2.8)	134 26 (19.4)
	25-<30	36 0 (0)	58 3 (5.2)	9 0 (0)	16 0 (0)	27 0 (0)	42 3 (7.1)
	30 - < 40	14 0 (0)	27 0 (0)	2 0 (0)	4 0 (0)	12 0 (0)	23 0 (0)
	≥ 40	2 0 (0)	2 0 (0)	0 0 (0)	0 0 (0)	2 0 (0)	2 0 (0)
	Total	163 4 (2.5)	335 57 (17.0)	36 0 (0)	85 12 (14.1)	127 4 (3.1)	250 45 (18)

Change from baseline in weight and BMI by BMI category (pooled data)

The pooled data for patients with a mean increase in weight and BMI from baseline to end of treatment were higher for quetiapine treated patients compared to placebo in each of the different BMI categories. (See Table 7).

Table 7 Change from baseline in weight and BMI by BMI category in pediatric studies D144C00149 and D144C00112 (pooled data)

BMI category (kg/m^2)		QTP		PLA	
	n	65		24	
Underweight BMI < 18.5		**Weight**	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	42.5 (7.5)	17.1 (1.2)	42.3 (10.2)	16.9 (1.2)
End of treatment	Mean (SD)	44.5 (7.9)	17.8 (1.5)	42.8 (10.0)	17.0 (1.3)
Change	Mean (SD)	2.0 (2.3)	0.7 (0.9)	0.5 (1.5)	0.2 (0.6)
Normal weight 18.5 ≤ BMI≤ 25	**n**	**181**		**90**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	57.1 (9.7)	21.5 (1.8)	58.3 (9.6)	21.6 (1.8)
End of treatment	Mean (SD)	58.9 (10.3)	22.0 (2.0)	58.6 (9.8)	21.7 (2.1)
Change	Mean (SD)	1.8 (2.4)	0.6 (0.9)	0.4 (2.5)	0.1 (0.9)
Overweight 25 ≤ BMI≤30	**n**	**60**		**33**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	72.4 (10.7)	27.4 (1.4)	69.5 (8.3)	26.8 (1.3)
End of treatment	Mean (SD)	73.5 (11.0)	27.7 (1.7)	68.8 (7.5)	26.4 (1.3)
Change	Mean (SD)	1.1 (2.6)	0.3 (1.0)	-0.8 (2.7)	-0.3 (0.9)
Obese BMI ≥ 30	**N**	**34**		**18**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	92.4 (14.5)	33.5 (3.1)	96.7 (11.3)	34.8 (3.6)
End of treatment	Mean (SD)	94.9 (16.7)	34.1 (3.4)	97.4 (12.5)	34.9 (3.9)
Change	Mean (SD)	2.5 (3.8)	0.7	0.7 (2.8)	0.1 (1.1)

5.1.2 Longer-term open label pediatric data

5.1.2.1 D1441C00150

Study 150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study 112) and in children and adolescents with bipolar I disorder (continuing from Study 149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Adverse event data

Adverse events of weight increased were reported for 51 patients (13.4%) in the safety population, including 24 patients (18.6%) who were treated with placebo during the acute feeder studies and 27 patients (10.8%) who received quetiapine during the acute feeder studies. Nearly all adverse events of weight increased were judged related to study medication by the investigator; three adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 8.

The mean change in weight for all schizophrenia patients who enrolled from OL baseline to final visit was 3.3 kg; the increase in weight was greater in patients who were treated with placebo (4.3 kg) compared with quetiapine (2.8 kg) during the acute feeder study. The change in mean weight from DB baseline was 4.6 kg for schizophrenia patients.

The mean change in weight for all bipolar I disorder patients who enrolled from OL baseline to final visit was 4.0 kg; the increase in weight was greater in patients who were treated with placebo (5.5 kg) compared with quetiapine (3.2 kg) during the acute feeder study. The change in mean weight from DB baseline was 5.3 kg for bipolar I disorder patients.

The mean change in weight for all patients who enrolled in trial 150 (n=380) from OL baseline to final visit was 3.7 kg; the increase in weight was greater in patients who were treated with placebo (4.9 kg) compared with quetiapine (3.0 kg) during the acute feeder studies. The change in mean weight from DB baseline was 5.0 kg for the total population. The mean change in weight for patients (from OL baseline) who completed 26 weeks of treatment with quetiapine (n= 241) was 4.4 kg.

Table 8 Study 150: mean changes from baseline to the final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.34	113	64.8	19.18	175	65.7	18.22
Change from 112 DB BSLN	62	4.1	8.46	113	4.8	10.75	175	4.6	9.98
Change from 150 OL Baseline	62	4.3	6.90	113	2.8	10.07	175	3.3	9.08
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.85	136	64.5	18.43	200	65.8	19.61
Change from 149 DB BSLN	64	5.8	6.42	136	5.1	5.66	200	5.3	5.90
Change from 150 OL Baseline	64	5.5	5.81	135	3.2	4.75	199	4.0	5.21
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.26	249	64.7	18.74	375	65.7	18.95
Change from DB BSLN	126	5.0	7.50	249	5.0	8.34	375	5.0	8.06
Change from 150 OL Baseline	126	4.9	6.38	248	3.0	7.64	374	3.7	7.28

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial 150, the mean change in weight from baseline was 4.4 kg. In these patients, the average percentiles at baseline and 26 weeks, respectively, were 64.0% and 64.7% for weigh, 49.4% and 49.0% for height, and 66.3% and 67.7% for BMI.

Patients with ≥ 7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 9). The incidence of ≥7% weight gain was higher in patients who were treated with placebo (39.4%) compared with quetiapine (33.7%) during the acute feeder studies.

In the schizophrenia population, 29.1% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was similar in patients on quetiapine in the Study 150 who were treated with placebo (30.6%) compared with quetiapine (28.3%) during the acute feeder studies.

In the bipolar I disorder population, 41.3% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was higher in patients on quetiapine in the Study 150 who were treated with placebo (47.7%) compared with quetiapine (38.2%) during the acute feeder studies.

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥ 7 % increase in weight from baseline.

Table 9 Study 150: Patients with ≥ 7% weight gain (Summary safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

5.1.3 Additional analysis of Pediatric data

5.1.3.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI) since in BMI, the weight is adjusted for height. (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z score taking into consideration the age and gender of the subject. Z scores are able to show how different a child's weight or BMI is from the average children with the same height. (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z score of 0.5 over any duration of time. (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for bipolar-I patients to the final visit and end of treatment are similar for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the total DB baseline to the end of treatment and final visit were higher in the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores for each visit are plotted over time for the treatment of placebo, quetiapine and total for study 150 (See Appendix A).

Table 10 Study 150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.20	113	**-0.1**	1.40	175	**0.0**	1.34
Week 26	41	0.4	1.05	86	0.1	1.22	127	0.2	1.17
Final Visit	62	**0.5**	1.03	113	**0.2**	1.25	175	**0.3**	1.19
149 DB Baseline	67	**1.0**[a]	1.01	138	**0.9**[a]	1.06	205	**0.9**[a]	1.04
Week 26	37	1.2	0.97	77	1.2	0.96	114	1.2	0.96
Final Visit	63	**1.2**	0.95	135	**1.0**	1.03	198	**1.1**	1.00
DB Total Baseline	129	**0.6**	1.15	251	**0.4**	1.32	380	**0.5**	1.27
Week 26	78	0.8	1.08	163	0.6	1.22	241	0.7	1.18
Final Visit	125	**0.9**	1.04	248	**0.7**	1.21	373	**0.7**	1.16

[a] The mean BMI Z score at baseline is much higher for the 149 population

Schizophrenia patients with ≥ 0.5 shift in standardized BMI Z score

A higher percentage of quetiapine treated patients (15 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to placebo treated patients (3 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (27.4 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (21 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (24.2 % at EOT) vs. prior quetiapine treated patients (14.2 % at EOT) from the OL baseline for schizophrenia had ≥ 0.5 shift in standardized BMI Z score. (See Table 11).

Table 11 Patients with ≥ 0.5 shift in standardized BMI Z score in Study 112 and patients from study 112 extending into Study 150

Occurrence	Double blind Study 112		Study 112 to OL Study 150		
Time/baseline	All Quetiapine	Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment /DB	22/147 (15)	2/75 (3)	24/113 (21)[a]	17/62 (27.4)[a]	41/175 (23.4)[a]
End of Treatment /OL			16/113 (14.2)[b]	15/62 (24.2)[b]	31/175 (18)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150

Patients with ≥ 0.5 shift in standardized BMI Z score in Study 150 by indication

A higher percentage of schizophrenia patients, (who enrolled in study 150) treated with prior placebo (27.4 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.2 % at EOT) from the DB baseline of study 112. (See Table 12).

A higher percentage of schizophrenia patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (14.2 % at EOT) from the OL baseline. (See Table 12).

A similar percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.5 % at EOT) form the DB baseline of study 149 (See Table 12).

A higher percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (8.3 % at EOT) form the OL baseline (See Table 12).

Table 12 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by indication

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Patients with ≥ 0.5 shift in standardized BMI z score in Study 150 by age group

A similar percentage of ≤ 12 years old patients (who enrolled in study 150) treated with prior placebo (28 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (25 % at EOT) from the DB baseline (See Table 13).

A higher percentage of ≤ 12 year old patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (8.6 % at EOT) from the OL baseline (See Table 13).

A similar percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (22 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (20.1 % at EOT) from the DB baseline (See Table 13).

A higher percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (21 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (11.7 % at EOT) from the OL baseline (See Table 13).

Table 13 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by age group*

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.2 Adult clinical trial data

An analysis of SEROQUEL and long-term weight gain was performed. This retrospective study assessed the magnitude and pattern of weight change during long-term treatment with SEROQUEL. Analysis of data collected from patients with schizophrenia, who were treated with SEROQUEL in AstraZeneca clinical trials from July 1993 to May 1999, was performed.

Weight changes were analyzed in patients treated for 12 weeks (± 4 days), 52 weeks (±30 days), and 104 week (±45 days). To be eligible for inclusion in the analyses patients had to have weight measurements recorded at baseline, and at the relevant time points (12, 52, 104 weeks). The primary cohort was the 52-week group.

All concomitant medications were stopped before entry into the trials, but in some concomitant antipsychotic medication was permitted during the open-label extension phases. Data were analyzed for all patients receiving quetiapine, and for the subgroup of patients who received quetiapine monotherapy.

In total, 378 patients with schizophrenia had weight data available after treatment with quetiapine for 12 weeks; of these 340 received quetiapine Monotherapy. Mean (95% CI) weight gain was 1.46 (0.98, 1.95) kg for all patients and 1.48 (0.98, 1.99) kg for the monotherapy group. Median weight gain was 1.15 kg for all patients and 1.36 kg for the monotherapy group.

In total, 352 patients with schizophrenia had weight data available after treatment with quetiapine for 52 weeks; of these 297 received quetiapine Monotherapy. Mean (95% CI) weight gain was 3.19 (2.27, 4.11) kg for all patients and 3.59 (2.57, 4.61) kg for the Monotherapy group.

In total, 166 patients with schizophrenia had weight data available after treatment with quetiapine for 104 weeks; of these, 143 received quetiapine Monotherapy. Mean (95% CI) weight gain was 5.16 (3.62, 6.70) kg for all patients and 5.59 (3.98, 7.20) kg for the Monotherapy group. Median weight gain was 4.1 kg for all patients and 4.5 kg for the Monotherapy group.

Ninety-seven patients with schizophrenia had bodyweight data available at Weeks 12, 26, and 52. These data indicate that during one year of treatment with quetiapine, 69% of the total mean weight gain occurred within the first 12 weeks and 96% in the first 26 weeks. Similarly, data from the 12, 52, 104 week cohort (n = 5) indicated that 62% of the total weight gain occurred in the first 12 weeks of treatment. Furthermore, 99% of weight gain occurred in the first year, with negligible weight change between one and two years.

The results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship. (Brecher et al 2007)

5.2.1 Acute placebo-controlled trials

The data below is taken from the cumulative clinical trial database (v15) for quetiapine. In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). (see Table 14).

The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 % (see Table 15).

Table 14 Incidence and relative incidence for weight gain risk, adult subjects – all Placebo-controlled trials

Risk	QTP incidence rate N=7481	Pla incidence rate N=3501	Relative incidence compared to Pla	Relative incidence 95% CIs	
	n (%)	n (%)	Ratio	Lower	Upper
Weight gain (> 7% increase)	721 (9.6)	134 (3.8)	2.5	2.1	3.0

CI Confidence interval. Pla Placebo. QTP Quetiapine.
Numbers in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001and D1447C00134.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_pla_ctr.SAS. Programmer: F Strömberg. 2008-06-18 15:23. DB version: 15

Table 15 Incidence weight gain, adult subjects – all trials

Risk	QTP incidence rate N=22382
	n (%)
Weight gain (> 7% increase)	4070 (18.2)

Number in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_all.SAS. Programmer: F Strömberg. 2008-06-26 9:14. DB version: 15

6. HOUSE SAFETY DATABASE OR POST-MARKETED USE

The post-marketing data was not reviewed for this topic.

7. DISCUSSION

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not acutal weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

8. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

Brecher et al 2007
Brecher M, Leong RW, Stening G, Osterling-Kiskinen L, Jones MA. Quetiapine and long-term weight change: A comprehensive data review of patients with schizophrenia. J Clin Psychiatry 2007; 68: 597-603.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 S-048

AstraZeneca Pharmaceuticals LP
Attention: Kathryn Bradley
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bradley:

We acknowledge receipt of your supplemental new drug application dated and received December 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets.

This "Changes Being Effected" supplemental new drug application provides for revised labeling to include new safety information for both adult and pediatric patients.

We have no objection to your submission of the new safety information pertaining to the clinical trials as a CBE supplement. However, the Division is requesting that you reformat the information for better integration in the overall label prior to your intended implementation on January 4, 2009. Specifically:

1. Place the pediatric safety information in the relevant sections of labeling with the adult data rather than separately in sections 5.19 and 8.4. For example, the proposed pediatric data in the section 8.4 subtitled "Changes in Thyroid Function Tests" should be placed at the end of section 5.10 (Warnings and Precautions: Hypothyroidism). The same principle applies to other pediatric safety information that already has adult data included prominently.
2. The weight gain signal is significant for both adult and pediatric populations and should be elevated to the Warnings and Precautions section rather than the vital signs section (the latter section could refer back to the information in Warnings and Precautions section) with inclusion of data for both populations. In fact, the data for weight change, glucose changes, and lipid changes from the clinical trials, both adult and pediatric, need to be elevated to the Warnings/Precautions section of labeling. Please see the format used in the currently distributed label for another antipsychotic drug, i.e., Zyprexa, for the correct format for this information.
3. The safety data for Increases in Blood Pressure is an unexpected signal and there is currently no similar adverse event signal for the adult population. Because of this unexpected and clinically significant signal that may be specific to the pediatric population, this safety data should be included in a separate section in Warnings and Precautions. Please offer your rationale for this unusual finding.

4. For each section describing pediatric safety signals, the following statement should be included "Safety and effectiveness of SEROQUEL have not been established in pediatric patients and SEROQUEL is not approved for patients under the age of 18 years".
5. Please replace your proposed Hyperprolactinemia statement with the standard language now used for more recently approved atypical antipsychotic agents, e.g., Invega. Any actual clinical trials data regarding prolactin elevation should, of course, be data for quetiapine, including the pediatric data.
6. All pediatric safety data and the other changes we are requesting for Seroquel should be included in revised labeling for Seroquel XR as well.

The above requested changes should be implemented immediately, and they should be submitted as an amendment to your pending supplemental application to the Seroquel NDA and as an original supplemental application to the Seroquel XR NDA, 22-047, within 30 days from the date of this letter, or notify FDA that you do not believe these changes are warranted, and submit a statement detailing the reasons. If you wish to have our prior comment on your alternative proposal in response to these requests, we would be happy to provide such comment.

Please note that your proposed labeling language in the above referenced CBE is under continuing review by the Agency. Please also note that the Division is currently reviewing your metabolic data submission and the pediatric efficacy supplements submitted under this NDA (S-045 and S-046). We will be providing further labeling comments, if any, and will take final action on these submissions when reviews are completed.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
12/18/2008 04:06:08 PM

EXHIBIT 33

Diabetes Information

Prevalence in the US population			
	General population	People with schizophrenia	People with bipolar disorder
diabetes	6%-7%[1,2]	13%[3]-18%[4]	10%[5]-26%[3]
smoking	34%-39%[6,7]	74%-90%[8]	35%*-55%[9,10]
obesity (BMI ≥ 30)	20%[2]-31%[11]	40%-60%[12]	30%[3]

*For mania

Testing and Monitoring Patients on Atypical Antipsychotics

- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness[13]
- ADA recommends that patients' weight be reassessed at 4, 8, and 12 weeks after starting on an atypical antipsychotic, and then quarterly during routine visits[14]

Patients Starting on an Atypical Antipsychotic[13]		
With an established diagnosis of diabetes	With risk factors for diabetes	Any patient
■ Monitor regularly for worsening of glucose control	■ Test fasting glucose at the start of treatment ■ Test fasting glucose periodically during treatment	■ Monitor for symptoms of hyperglycemia

Diabetes Risk Factors for Asymptomatic Adults[15]	
■ Age >45 years	■ Hypertension (BP ≥140/90 mmHg)
■ BMI >25 kg/m^2	■ HDL–C <35 mg/dL and/or triglycerides >250 mg/dL
■ Habitual physical inactivity	■ Polycystic ovary disease
■ First-degree relative with diabetes	■ IGT or IFG on previous testing
■ High-risk ethnic group (eg, African American, Latino, Native American, Asian American)	■ Other clinical conditions associated with insulin resistance (eg, acanthosis nigricans)
■ Having delivered a baby weighing >9 lb or having been diagnosed with gestational diabetes	■ History of vascular disease ■ History of smoking

See Important Safety Information on reverse side and accompanying full Prescribing Information.

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

Diabetes Information

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population[13]
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant[14]
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information[16]
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

Important Safety Information

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy with lithium or divalproex, and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL.

Precautions include the risk of seizures, orthostatic hypotension, and cataract development.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

See accompanying full Prescribing Information.

References: 1. CDC. National diabetes fact sheet. Available at: http://www.cdc.gov/diabetes/pubs/estimates.htm. Accessed April 7, 2005. 2. Mokdad AH, Bowman BA, Ford ES, et al. *JAMA*. 2001;286: 1195-1200. 3. Regenold WT, Thapar RK, Marano C, et al. *J Affect Disord*. 2002;70:19-26. 4. Bushe C, Holt R. *Br J Psychiatry*. 2004;184(suppl 47):s67-s71. 5. Cassidy F, et al. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry*. 1999;156:1417-1420. 6. Gopalaswamy AD. Smoking in chronic schizophrenia. *Br J Psychiatry*. 1986;149:523. 7. Masterson E, O'Shea B. Smoking and malignancy in schizophrenia, *Br J Psychiatry*. 1984.145:429-432. 8. Forchuk C. Schizophrenia and the motivation for smoking. Available on-line at: http://www.findarticles.com/p/articles/mi_qa3804/is_200204/ai_n9032259/print. Accessed on April 22, 2005. 9. Grant BF, et al. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2004;61:1107-1115. 10. Ucok A, et al. Cigarette smoking among patients with schizophrenia and bipolar disorders. *Psychiatry Clin Neurosci*. 2004;58:434–437. 11. AOA. AOA Fact Sheets: obesity in the U.S. Available on-line at: http://www.obesity.org/subs/fastfacts/obesity_US.shtml. Accessed May 2, 2005. Cigarette 12. Catapano L, Castle D. Obesity in schizophrenia: what can be done about it? *Australasian Psychiatry*. 2004;12:23-25. 13. SEROQUEL® (quetiapine fumarate) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2004. 14. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596-601. 15. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2005;28(suppl 1):S4-S36. 16. Data on file, DA-SER-30.

AstraZeneca

AstraZeneca Pharmaceuticals LP

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

EXHIBIT 10

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalcyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Could the interaction with age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like?
For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Shold we get together to chat?

Thanks
Lisa

EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE:

SEROQUEL PRODUCTS LIABILTY LITIGATION

CASE NO. 6:06-MD-01769-ACC-DAB

MDL DOCKET NO. 1769

May 28, 2008

Confidential Videotaped Oral Deposition of MARTIN BRECHER, M.D., D.M.Sc., MBA, held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, Philadelphia, Pennsylvania beginning at approximately 9:00 a.m., before Ann V. Kaufmann, a Registered Professional Reporter, Certified Realtime Reporter, Approved Reporter of the U.S. District Court, and a Notary Public.

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
Philadelphia, Pennsylvania 19103
877.370.3377

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merged entity for six to eight months when I joined.
Q. And you mentioned that Wayne Geller came over from Janssen a little bit after you; correct?
A. That's right.
Q. Was there any connection between you going to AstraZeneca and Dr. Geller going to AstraZeneca or was it coincidence?
A. I had given Wayne Geller's name to the director of safety as someone who was a good worker.
Q. Okay. So was he recruited to work at AstraZeneca because of your recommendation?
A. Possibly. I remember a conversation with Vikram Dev. I don't -- and I don't think I would have offered. I think, my best recollection, he would have asked, do you know. So it would have been along the lines, do you know any good safety people.
And assuming that was the

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question, I would have said, Yeah, Wayne Geller.
Q. Okay. You trusted his judgment?
A. Yes, I did.
Q. He wasn't fired from Janssen, was he?
A. No.
Q. When you started in December of 1999, did you take some period of time to educate yourself about Seroquel and what had happened previously?
A. I tried.
Q. Did you take a look at what studies were out there that had been done that were successful studies?
A. I remember reviewing the submissions to the FDA and the European countries.
Q. Okay. Did you review the studies that were failed studies?
A. I was aware of them.
Q. Okay. Did you review any

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cursed studies?
A. Sorry? Any?
Q. Cursed studies.
MR. McCONNELL: Objection to form.
A. I don't know any cursed studies.
Q. Okay. Do you know any studies that you reviewed where smoke and mirrors were used to present them?
MR. McCONNELL: Objection to form.
A. I don't -- I heard that expression in one context, I don't remember which, but that -- but certainly in my review of the documents when I joined the company, it did not include a reference to smoke and mirrors.
Q. Do you know about study 15?
A. Pardon?
Q. Do you know about study 15?
A. Yes.
Q. What was study 15?

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A. Study 15 was a long-term study comparing three doses of Seroquel to haloperidol for the prevention of relapse in schizophrenia.
Q. Okay. And when did you first become familiar with study 15?
A. I must have read about it in reviewing the submission documents to the FDA and the EEU because it was in the package.
Q. Okay. Did you ever review the weight gain data from study 15?
A. I can't say. I don't believe the weight gain -- I don't think there was a lot of weight gain data from study 15 because, as I understand now, only 28 patients actually completed a year of treatment.
Q. I'm going to show you what was previously marked as Schwartz Exhibit No. 41 and now is marked as Brecher Exhibit 3.
(Below-described document marked Brecher Exhibit 3.)

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BY MR. BLIZZARD:
Q. Do you see that this is an e-mail or an internal memorandum that's dated February 12, 1997?
MR. McCONNELL: Objection, foundation.
A. I'm sorry, your question again, please?
Q. Do you see this is an e-mail dated February 12, 1997? Actually, strike that.
Do you see this as an internal memorandum dated February 12, 1997?
A. Yes.
Q. It says here that it is from Richard Lawrence. Do you know who Richard Lawrence is?
A. I never met him, and his name has come up, but he was way before my time.
Q. Okay. Well, this looks like it's about almost three years before your time.

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A. That's right.
Q. It's regarding a U.S./Canada investigator meeting and study 15. Do you know anything about the U.S./Canada investigator meeting?
A. No.
Q. Did you review any of the that material when you came on board at AstraZeneca?
A. I don't recall ever seeing material specifically relating to the U.S./Canada investigator meeting.
Q. Do you see that this distribution of this e-mail went to Don Stribling?
A. Yes.
Q. Do you know who Don Stribling is?
A. I knew him when he worked in Japan. He once came to a meeting that we had with our Japanese collaborators. And he subsequently was the head of regulatory affairs.
Q. So he was pretty high up

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the corporate totem pole, wasn't he?
MR. McCONNELL: Objection to form.
A. I don't know what position he had in 1997.
Q. Well, when you knew him, he was fairly high up the corporate totem pole, wasn't he?
A. Yes.
MR. McCONNELL: Objection to form.
A. Yes. He was the --
Q. Let me try corporate ladder.
A. In his role as the head of regulatory affairs for the company, that's a responsible and senior position within the clinical development organization.
Q. Okay. Now, do you see in this -- first of all, that this was CC'd to a Lisa Arvanitis?
A. Yes.
Q. Do you see that? Do you

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know who Lisa Arvanitis is?
A. Lisa Arvanitis was the medical leader for Seroquel probably at the time of the writing of this e-mail. She had been gone from the company for some time when I arrived.
Q. So was she in your job as of the time of this e-mail?
A. To the extent -- I think she was the medical leader for Seroquel at the time. I think that's a fair guess on my part. Obviously I wasn't there, but I was aware that Lisa Arvanitis was leading the quetiapine effort, and so I think that she had a job roughly analogous to mine.
Q. Okay. Do you see where it says in the e-mail here that: "I am not 100% comfortable with this data being made publicly available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke and mirrors' job!" Do you see that?

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Q. Okay. So he wasn't happy, was he?
MR. McCONNELL: Objection to form.
A. Well, I think his e-mail speaks for itself. I think he was -- expressed concern, I would say. As he said he questioned the rationale for distributing it to the marketing people for, quote, informal review.
Q. And your response is to say I don't see a problem with marketing knowing where we're going; correct?
A. Yes.
Q. Were you trying to lobby the marketing people to support you in the decision to keep "limited" in the core data sheet?
A. I don't think that's where that e-mail is going at all. I think all I'm saying there is I didn't see a problem with marketing knowing what our position was. And that's what I said before, before you showed me this

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document, I said I didn't see a problem with the marketing people seeing the discussion documents prior to the meeting.
Q. Well, do you see a problem with soliciting their comments to the discussion document?
A. I think that this -- it would be inappropriate if a drug safety person would ask for marketing comments, and I don't think that ever happened. This --
Q. Well, you were -- I'm sorry. Go ahead.
A. This discussion document, as I said, immediately after you showed it to me, is unusual in that it's being produced by a member of the Seroquel team. And I have offered a possible explanation why. And clearly the writer wanted to get marketing's view on the content.
Q. Well, did you -- you were on the e-mail that was sent by Emma

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Witch soliciting comments of the marketing folks and others; correct?
A. Yes.
Q. Okay. Did you say "Whoa, Emma, don't go submitting this for comment to the marketing people"?
A. I did not.
Q. Did you tell her in any way that she should hold off sending this to marketing for comment because it was inappropriate?
A. I did not.
Q. Now, the discussion -- the SERM meeting that occurred in June of 2000, did you attend that in person?
A. The June 2000 SERM, yes.
Q. Where did it occur?
A. It must have occurred in Wilmington.
Q. Okay. But you specifically have a memory of being there for the meeting?
A. Not a strong one. You know, it's clear from the earlier

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document that you showed me that I was there. And I don't have a vivid recollection of the meeting, but I do have a recollection of being there.
(Below-described document marked Brecher Exhibit 18.)
BY MR. BLIZZARD:
Q. I have handed you Exhibit No. 18, and it has a number of handwritten notes on it. Are those -- is that your handwriting?
A. Yes.
(Below-described document marked Brecher Exhibit 19.)
BY MR. BLIZZARD:
Q. Before I get to what that says, let me mark as Exhibit 19 to your deposition -- are these draft minutes of a meeting in July of 2000?
A. This is -- are you talking about 19?
Q. Yes.
A. They are draft minutes.
Q. Okay. Is that a -- are the

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minutes prepared by Emma Witch?
A. Yes.
Q. And is Emma Witch shown as an attendee at this meeting?
A. Yes.
Q. Are these other people involved in this meeting, SERM members?
A. Wayne is a SERM member. I don't know whether or not Paul Duffy would have participated in SERM. He was a -- he is a toxicologist and was involved in the preclinical work with Seroquel.
Q. Okay. So these meeting minutes do not reflect the minutes of SERM, do they?
A. No.
Q. Okay. This is a separate meeting that relates to the preparation of the FDA response to the -- on the diabetes issue?
A. Response to the FDA, right.
Q. Okay. Well, we will get to that in a minute then.

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Take a look at the discussion document for Seroquel. These handwritten notes that were made on this document, Exhibit 18, were -- when were those made?
A. You know, I'm not sure what document this is. I can guess, but perhaps you could tell me.
Q. Well, as the title says, "Diabetes Mellitis, Diabetic Ketoacidosis, Non-Ketotic Hyperosmolar Coma, and Hyperglycaemia." And it is a discussion document regarding Seroquel; correct?
A. Yes.
Q. And it's prepared by Wayne Geller; correct?
A. Yes.
Q. I believe that this document was prepared in advance of the SERM meeting and was discussed at the SERM meeting. That's my belief. Do you recall that?
A. Are you referring to the

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June 2000 SERM meeting?
Q. Yes.
A. That's what I think as well. I just don't see a date on this document. But looking at the cover and just quickly glancing through the interior, I think this is the discussion document or a draft of it prepared for this -- as a discussion document for the June 2000 SERM.
Q. Okay. What I would like for you to do for me is to read your handwriting. Sometimes I can read it; sometimes I can't. And I want to make sure we have an accurate rendition of your handwritten notes from this meeting.
First, on the first page at the top, what does that say?
A. Where it says 1)?
Q. Yes.
A. That's angioedema.
Q. What have you crossed through at 2)?

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A. I think it's -- "limited" is crossed out.
Q. Okay. What's No. 3)?
A. It looks like "hyperglycemia" and "diabetes."
Q. Okay. Do you know why "limited" is crossed out in No. 2)?
A. I can't recall.
Q. Is it possible it relates to the weight gain issue?
A. I have no recollection what I was thinking when I wrote these notes.
Q. Okay. So all you can do at this point is read them to me; correct?
A. That's right.
Q. Okay. What does the note on the right-hand margin say that says "OS"?
A. I think that's "US."
Q. Okay.
A. That makes more sense to me. And I think to the right of that it says "involuntary movements."
Q. Okay. And then it says

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"CDS"?
A. "Discussion."
Q. What does "CDS" stand for?
A. Core data sheet.
Q. Okay. Then on the first page out on the left-hand side under the heading "All Findings Presented in This Document Are to Be Subject to Further Consideration at SERM," does it say "6 cases"?
A. Yes.
Q. What does it say beneath that?
A. Below that?
Q. Yes.
A. I can't make out the first word. And then it says "time to onset new diabetes 0.5 months." Oh, "Median." "Median time to new onset diabetes 0.5 months."
Q. Okay. And then in the middle of that, just to the right of that note, what does that say? It says "Wayne" at the top and that is

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underlined?
A. Yeah. "Page 8, 2240 base rates." And then it says something that doesn't make sense to me, gdv or gov. I don't know what that means --
Q. Okay.
A. -- with a question mark.
Q. And then over on the right-hand margin, what does that say?
A. "Emma, MJ - dose response." MJ would be Martin Jones. And then below that --
Q. Is Emma Emma Witch?
A. Probably. I think that we also had an Emma Westhead, but -- so I don't know which Emma this is referring to.
Q. Okay.
A. And then "Geert - 6 cases, conclusions."
Q. So what does "Geert" refer to?
A. Geert would refer to Geert deVriese, who was the global product

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director.
Q. Okay. Do you know what the "6 cases" references?
A. You know, I don't know if it's the same six cases referred to on the left.
Q. Okay. And what does it say beneath that? There's an arrow pointing down.
A. I can't quite read the first word. And then the second word is "CDS in line with US PI?" Oh, "bring." I think it says "Bring CDS in line with US PI?"
Q. Okay. So there was some question about whether -- or somebody was raising the question of whether the CDS should be brought in line with the U.S. package insert; correct?
A. I don't know if that was my question or someone else's question.
Q. Okay. And then underneath that what does it say?
A. "Conclusion: Keep issue

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under review."
Q. And then under -- on the bottom of the page what does it say?
A. "Of 10 cases from clinical trials," arrow "each source?"
Q. Second page up at the top?
A. "RIS labelled for diabetes, DKA."
Q. And that's diabetic ketoacidosis?
A. That's what the DKA would stand for.
Q. Okay. Under -- right next to the "Introduction" section, what does that say?
A. "Criteria used in this assessment." It looks like "FBS," which would be fasting blood sugar, "greater than 126 2 hour post, 75 grams greater than 200."
Q. Okay. Can you interpret that note?
A. Yeah. I think that -- what I think it means, without confirming it

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from the text, is that the criteria used in the assessment was either a fasting blood sugar greater than 126 or a two-hour glucose value following 75 grams of glucose -- in other words, a glucose tolerance test -- with a value greater than 200.

Q. Okay. If you go turn the page to the next note that we have. It looks like it's over on Page 6.

Okay. What does that say?

A. On the top?

Q. Yes.

A. "No attribution." And then to the right of that it says "16, SPONT," probably referring to -- standing for spontaneous; "10 clinical" -- "10 CLIN trials," referring to ten clinical trials; and "2 lit reports." So what this is referring to is 16 spontaneous reported adverse events, ten clinical trial reports, and two reports in the literature, and they are pointing to no attribution.

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Q. Okay. Under "CLINTRACE Database (In House Safety Data)," there's a note that says "9 cases"?

A. "9 cases new onset, 4 DKA, 2 new onset, 2 worsening." And then below that is "NKHOC-0." And NKHOC would stand for nonketotic hyperosmolar coma.

Q. And then you've got a star next to this particular description of this event of a 43-year-old male with a history of mental illness who developed new onset diabetes. Do you see that?

A. Yes.

Q. Do you know why it was starred?

A. No. And I'm just curious whether I starred other cases.

Q. I think you did. Look over at the next page. Do you see that?

A. Yes.

Q. And this particular case is a diabetes case with weight gain; correct?

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A. Yes.

Q. And you starred that?

A. Yes.

Q. And do you know why you starred it?

A. No.

Q. I assume that you starred things that were important to you; is that correct?

A. Presumably. I certainly don't -- I'd have to pore over this document to see what were the common features of the starred cases. I don't recall that now.

Q. Okay. Look over at the next page. Do you see that there's a starred event on this page as well?

A. Yes.

Q. And the next page, "Loss of Diabetic Control, Tooth Pain, Insomnia"?

A. Yes.

Q. Do you see that that event is starred?

A. Yes.

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Q. If you look over at Page 11 --

A. Yes.

Q. -- do you see a star there?

A. Yes.

Q. Do you know anything about why that star is there?

A. I don't recall the principle leading to the starring of cases.

Q. Okay. If you look over on Page 15, there's a star next to another case of hyperglycemia?

A. Yes.

Q. Okay. On Page 16 --

A. Yes.

Q. -- could you read that handwriting for us?

A. It says "Median?" Below that "time to onset." There's text that reads "The former patient reportedly lost 30 pounds," and then there's a line from that going to a handwritten note saying "Type 1 - pattern."

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Below that it says "2 cases of DKA - weight gain associated." And then below that there's a -- it says "criteria greater than 110" -- it looks like greater than 110 pounds, but I'm not sure what that means.

Q. This relates to reports of hyperglycemia.

A. Oh, I'm sorry. I can -- this one on Page 16 on the bottom that the arrow says "criteria greater than 110 fbs," it's for fasting blood sugar.

Q. Okay. And the last page, Page 17, what does the note at the top say?

A. "Note, Wayne impressed by 2 physicians noting diabetes onset with dose increase."

Q. Okay. So does that note reflect that Dr. Geller was impressed with the dose-response?

A. I don't think that represents a dose-response so much as exactly what it says, that two

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physicians noted diabetes onset following a dose increase. I don't think that indicates a dose-response.

Q. It indicates that the diabetes onset occurred after the dose was increased; right?

A. That's right. It is different from a dose-response.

Q. Okay. The next item in the middle of the page says what?

A. "Usually no baseline blood glucose. 7 taking drugs associated with diabetes. Some reports - scant information" -- "scant inf" meaning scant information -- "no positive de," which means no positive dechallenge or rechallenge.

Q. What's the next note say?

A. "Seroquel may cause impaired glucose regulation in some individuals. No signal of Type 1 ie no negative impact on insulin production."

Q. Okay.

A. Well, that -- "Discussion:

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No positive re,de challenge. No baseline CHO," referring to no baseline glucose. "Low number of cases for a common condition."

That's actually an important point because diabetes is very common. And my comment here, I think, reflects the view that this is a small number of cases for an illness as common as diabetes, given the exposure that we had by 2000.

"No mechanism of effect."

On the right it says "For my part only 4 cases of DKA speaks to absence of diabetogenic effect."

Below that: "Other patients: 1., will get long term data from olanz trial. 2., will" --

Q. What's "olanz trial"?

A. That would refer to olanzapine, but I'm not -- I don't know what olanzapine trial I was referring to, unless -- probably given that it was 2000, it could either have referred to

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the long-term trials that Lilly conducted or to the long-term trial that Janssen conducted.

And then below that, "will" --

Q. "Know more?"

A. "Will" --

Q. -- "know more after response to FDA concludes."

A. I think so.

Q. I may have stared at it longer than you, so whatever you need to do to confirm it.

A. Yeah, I think that's right.

Q. Okay. So in looking at this, you made the -- when you started talking about this discussion down here below the line, you may have said, well, here are a couple of important points.

And then there's these comments above the line that you read without making a comment about it.

Is it your memory, from looking at this now, that the points

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metabolism disorders. Dear Wayne, thank you for yoy fax" -- I guess that is supposed to be "your fax" -- "which I sent to the local authorities."
A. Yes.
Q. And when he actually faxed it to her, if you look at the -- Geller's communication on Page 2, do you see where he says: "Hi, Dorothee. The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once." Do you see that?
A. Yes.
Q. And then she sends back and says thanks for the fax; correct?
A. Yes.
Q. Okay. So, again, Dr. Geller is offering to sign this document before faxing it; right?
MR. McCONNELL: Objection to form.
BY MR. BLIZZARD:

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Q. Let me rephrase that. Dr. Geller is offering to sign the document that was attached; right?
MR. McCONNELL: Same objection.
A. Wayne is offering to sign the document.
Q. Right. and would that indicate to you, as a reasonable person who conducts business in the way that people typically conduct business, that that is not a draft?
MR. McCONNELL: Objection to form.
A. I was not involved with this correspondence between the Dutch and Wayne. And if Wayne was mistaken about his document, I don't think it matters whether or not he signed it or not. I don't know whether he knew it was a draft or not. And I can't comment. I just don't know his procedures well enough to comment on what's the implication of signing the

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document.
Q. What is the implication when you sign a document?
MR. McCONNELL: Objection to form.
A. When I sign a document, I usually -- it means that I wrote this document.
Q. It means you are taking responsibility for what's in the document; right?
A. Usually.
Q. And that's what it would mean here, wouldn't it, that he was taking responsibility as a global drug safety physician for the statements made in the document?
A. I want to say --
MR. McCONNELL: Excuse me. Objection to form.
A. I want to say two things: I don't know what Wayne -- was going through Wayne's mind and I don't want to comment on what it meant that he signed

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this document.
Moreover, if we get back to the document, I just don't feel that the arguments and the data that are in the document, particularly in the executive summary, are supporting the conclusions. So -- but, regardless, I don't think that -- I just can't comment -- I don't know whether this was the document that was mistakenly sent and I don't know --
Q. How do you --
A. I can't comment on the interaction between Wayne and the Dutch authorities because I was not involved in that transaction.
Q. Well, the e-mail that we just reviewed clearly indicates that the Dutch authorities were asking for an analysis of glucose metabolism and Seroquel; correct?
MR. McCONNELL: Objection to form.
A. The Dutch wanted a review

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of cases or an analysis of cases of diabetes and glucose metabolism that may or may not have been related to Seroquel.

Q. Right. And people within the marketing company over in the Netherlands asked Wayne Geller to submit a paper, and he offered to sign and faxed this safety position paper to them; correct?

MR. McCONNELL: Objection to form.

A. Wayne attempted to be responsive to a request and offered to sign a document.

Q. Now, the Dutch authorities weren't just acting as a single country in Europe at the time with respect to Seroquel, were they?

A. The Dutch was a reference member state.

Q. And the reference member state takes the lead for the entire European Union with respect to a

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particular drug that they are the reference member state for; right?

A. Right, for those states participating in the process.

Q. Okay. Do you know how many states in the European Union were participating in the process at the time in 2000 when this paper was sent to the Dutch authorities?

A. Well, account -- you know, there were new countries that joined the European Union over time, so I don't recall how many were there in 2000.

What I do know is that France was not a part of it and we had a separate registration procedure in England and Italy. So that the reference member state would have -- or that role as reference member state would have applied to the other Western European countries.

Q. Okay. Now, this document that we just read the conclusion of that was submitted to the Dutch, assuming it

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was the one that was submitted to the Dutch, that contained markedly different conclusions than the one that was given to the FDA, didn't it?

A. Well, I don't think I've looked at the FDA position paper today. And I think the position stated here is at variance with the FDA position paper.

Q. Okay. Well, we can look at the FDA position paper, and we will probably do that tomorrow. But I mean, without reading it, you know that the company did not write a paper to the FDA saying that there's reasonable evidence to -- that Seroquel can cause diabetes or hyperglycemia in certain individuals?

A. That's right.

Q. Right. In fact, you never sent this safety position paper of Dr. Geller to the FDA, did you?

MR. McCONNELL: Objection to form.

A. I don't think this safety position paper was sent to the FDA.

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Q. Right. Even today FDA doesn't have this safety position paper, does it?

A. And I don't think that this represents the view of AstraZeneca or the drug safety department at that time or, for that matter, now.

MR. BLIZZARD: Objection, nonresponsive.

BY MR. BLIZZARD:

Q. Now, let me ask you something that's really on a different subject now, and I think with that I'd like to maybe conclude for the day and we will save some additional time for tomorrow.

After the SERM meeting in 2007 there was a discussion document that was actually presented at the SERM meeting. And I have a copy of it. I'm not going to attach it today, but I think it's about 500 pages long. Do you recall that document?

A. It was a long discussion

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Q. Do marketing and commercial people at AstraZeneca have any role whatsoever in the SERM process?
A. They do not.
Q. Doctor, as part of the preparation for SERM, is safety data review and analyzed?
A. Yes.
Q. Could you explain to the jury what type of data is reviewed and analyzed as part of the SERM process?
A. The SERM reviews should include, and typically do include, the data from clinical trials, postmarketing surveillance and literature reviews, and sometimes the preclinical data as well.
Q. Is material from the global drug safety database reviewed as part of the SERM process?
A. Yes.
Q. Doctor, did AstraZeneca create the SERM process specifically to examine the glucose issue relating to Seroquel?

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A. Yes.
Q. They did that in the spring of 2000?
A. The SERM meeting for glucose was in June of 2000.
Q. Okay. Does AstraZeneca also use the SERM process at times for other drugs involving other issues?
A. The SERM process is used for all drugs, all marketed drugs at AstraZeneca.
Q. Does AstraZeneca convene SERMs only to respond to FDA requests?
A. No.
Q. In your experience, is the SERM process an effective tool to monitor the safety of the drug?
A. Yes.
Q. Why?
A. The SERM -- a SERM meeting is called whenever a question or an issue is raised around the safety of marketed medicine. So that could happen whether concerns are raised from within the

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company or in response to a request from a regulatory agency.
Q. Does the SERM process play a role in determining whether the core data sheet should be changed?
A. Yes.
Q. What is the core data sheet?
A. The core data sheet is the best description of the safety profile of the drug and represents the core items that have to be included in every product label. So it's that -- those facts about the safety of the drug that must be included in every label around the world.
Q. When AstraZeneca does convene a SERM, does the SERM always conclude that the core data sheet should be changed?
A. No, it doesn't.
Q. Does the SERM always conclude that the core data sheet should not be changed?
A. No, it doesn't.
Q. What explains the difference

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in those different kinds of decisions?
A. The critical point is whether the label accurately reflects the safety profile of the drug as we understand it.
Q. Does the SERM decision as to whether or not to change the core data sheet depend in any way upon the available data?
A. The SERM decision to change the core data sheet depends entirely on the data.
Q. Is the SERM process the only way that AstraZeneca monitors the safety of Seroquel?
A. No.
Q. What other procedures are in place at AstraZeneca to monitor the safety of Seroquel?
A. The drug safety department is monitoring safety on a continuous basis. And so are the clinical trials people. Clinical trials people are monitoring safety as the clinical trials

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are ongoing.
Q. Does anyone or any department at AstraZeneca monitor adverse events?
A. Primarily drug safety and also the clinical group.
Q. Does AstraZeneca submit periodic safety updates to the FDA?
A. Yes.
Q. In your experience, did AstraZeneca closely monitor the safety of Seroquel?
A. Yes.
Q. Now, you've discussed the SERM process generally. Are there documents that are associated with the SERM process?
A. Yes. Prior to a SERM meeting there's a discussion document. Following the SERM meeting there is either a position paper or justification document that's prepared.
Q. What's the purpose of a discussion document for SERM?

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A. A discussion document is written so as to inform the discussions at SERM of all the relevant facts.
Q. What's the purpose of a SERM position paper?
A. A SERM position paper is that -- is a paper that is written after a SERM meeting when the core data sheet is not changed on a particular issue. And it reflects the reasoning as to why the core data sheet is not changed on that point.
Q. Now, we talked about the FDA request in May of 2000 regarding glucose data. Did you participate in a SERM in 2000 regarding glucose issues?
A. Yes.
Q. Was there, in fact, a discussion at AstraZeneca at the SERM regarding glucose data?
A. Yes.
Q. What did that SERM conclude regarding whether there was reasonable evidence of an association between

Page 949

Seroquel and hyperglycemia or diabetes?
A. SERM decided to keep those issues under review, but not to change the core data sheet.
Q. What did SERM conclude as to whether there was a causal link between Seroquel and hyperglycemia or diabetes?
A. SERM did not conclude that there was a causal link between Seroquel and hyperglycemia or diabetes.
Q. What did SERM conclude in 2000 as to whether the data demonstrated reasonable evidence of an association between Seroquel and hyperglycemia or diabetes?
A. SERM concluded that the data did not show a reasonable evidence of an association.
Q. I want you to take a look at a document that the plaintiffs' lawyers put in front of you. It's Exhibit 18. Could we get a look at that?
Doctor, first of all, do you remember taking a look at Exhibit 18, I

Page 950

don't know if it was yesterday or the day -- I think it was the day before yesterday?
A. Yes, I remember.
Q. Could you turn to the last page, please?
A. Yes.
Q. Do you see handwritten notes on that page?
A. Yes.
Q. And that's your handwriting. Is that right?
A. Yes.
Q. I want to direct your attention to the handwritten notes that are underneath the typed section of the page. Do you see what I'm talking about?
A. Yes.
Q. All right. Do you recall testifying on Wednesday that those notes were your reflections on reading the document?
A. Yes.
Q. I want to get you to focus

Page 1015

questions now about another trial, it's one that you've been asked some questions about. I want to give you an opportunity to describe it to the jury. That's trial 125. Were you involved with trial 125?

A. Yes.

Q. Could you explain to the jury what trial 125 is?

A. Trial 125 was an effort by AstraZeneca to understand the effects of Seroquel on glucose metabolism. And to do that we used a more sensitive assay even -- than even the fasting glucose. We used the glucose tolerance test. That's very important because the glucose tolerance test becomes abnormal earlier in the course of diabetes than the fasting blood sugar so it was a sensitive test for the emergence of diabetes. We --

Q. Would it be -- I'm sorry, keep going.

A. We measured the area under the curve for the two hours of the

Page 1016

glucose tolerance test, and that, too, is a sensitive measure of whether there's an effect of a drug on glucose regulation. That was -- that's one important point.

The second important point was that we hospitalize the patients overnight both at baseline at week 12 and at week 24. And, therefore, we could be sure or as sure as one could reasonable want that the patients had not eaten prior to the exam both at baseline and at week 24.

Third, we were able to find patients who had not been previously exposed to atypical antipsychotics, so we were measuring -- we were studying relatively naive patients, and so we were able to look at results independent of what the patients had been on before. And lastly, the study was a long study, it was 24 weeks, and so we were able to have a good assessment of what the prolonged effect of treatment was on patients' glucose metabolism.

Page 1017

Q. Would it be absolutely accurate to describe trial 125 as a diabetes study?

A. No, it was not a diabetes study. It was an attempt to look at the effects of Seroquel on glucose metabolism measured by the two-hour glucose tolerance test.

Q. I just asked you about whether you can call 125 a diabetes study. Are there any ethical constraints to conducting a study that a scientist would actually be able to call a diabetes study?

A. I think it will depend on the design. There are a lot of different design possibilities, and one -- it would depend -- you know, ethical issues in the study would depend on what was actually being done. One point about this study was that every patient received active medication. We could not use a placebo in this trial because it would have been unethical to deprive patients of

Page 1018

medication for 24 weeks.

Q. Did the FDA or any other government body require AstraZeneca to conduct trial 125?

A. This was done on our initiative.

Q. When did AstraZeneca decide to start designing and planning trial 125?

A. The decision to conduct that trial was made in November 2002.

Q. Why then?

A. That was shortly after we had received a strong label change in Japan and -- requiring us to provide warnings and I believe a contraindication for the use of Seroquel in patients with diabetes. And we recognized that we did not have sufficient data to address concerns that other regulatory agencies might have, and, therefore, we wanted to collect data that could establish, as best we could, the fact that Seroquel did not cause diabetes or it is not

Page 1019

associated with glucose metabolism. And conversely, if Seroquel was associated with disorders of glucose metabolism, we wanted to know and we wanted to have the data in which to -- to be sure that that was the case so we could write the label accordingly.

Q. Why did AstraZeneca include Risperdal in trial 125?

A. We wanted to compare Seroquel to the two other comparators -- to two competitors on the market. We wanted to make sure that everybody got medication. The study was, therefore, able to compare all three drugs for their effects on glucose metabolism. And the study was able to look at the effects on each drug relative to the others as well as the change in each drug compared to baseline.

Q. Why didn't AstraZeneca start planning trial 125 prior to the year 2002?

A. We -- prior to the Japanese

Page 1020

action, we thought that our -- that the data that we had gathered, particularly the summary prepared for the FDA in August of 2000, had established that Seroquel was not associated with diabetes or abnormalities in glucose metabolism.

The Japanese regulatory action made it clear that our data was not persuasive, at least to them, and so we wanted to do two things as I just said, gather data that would allow us to persuade another regulatory agency that might have had a concern; or conversely, if there was than effect of Seroquel on glucose metabolism, we wanted to show and demonstrate it to ourselves.

Q. Prior to the planning of trial 125, in your mind, had the preclinical and clinical studies that supported the FDA initial approval of Seroquel revealed any evidence that Seroquel could cause glucose dysregulation?

A. The evidence that we had at

Page 1021

that time did not show -- did not provide any evidence that Seroquel caused diabetes or abnormalities in glucose regulation.

Q. Prior to the planning of trial 125, did the postmarketing surveillance data reveal evidence of a causal link between Seroquel and diabetes or hyperglycemia?

MR. PIRTLE: Leading.

THE WITNESS: The postmarketing data did not provide data showing a causal link between Seroquel and diabetes.

BY MR. McCONNELL:

Q. At the time that you started planning trial 125 in the fall of 2002, were you aware of any trial like it that any company had ever done?

A. I was not aware of any such trial. I thought this was innovative on our part.

Q. And in terms of numbers of patients, was trial 125 a large clinical

Page 1022

trial?

A. Yes. We enrolled 500 patients, a little over 500 patients, and that's a moderate to large size trial, especially for one that's going for 24 weeks.

Q. Did AstraZeneca consult with outside experts on the design of trial 125?

A. I believe so.

Q. Who did you consult with?

A. I'm not sure. I don't recall precisely who we consulted with. Probably -- I think we consulted with Woolf and Goldstein. I don't recall for sure. Possibly consulted with John Newcomer. Again, I don't recall for sure.

Q. Does it take a long time to get a trial --

A. Let me finish.

Q. I'm sorry, go ahead.

A. We probably also consulted with endocrinologists within the company.

Page 1031

A. That result is an important one. The primary result of the trial as stated in the protocol was the area under the curve from zero to two hours of the glucose -- of the glucose values following the ingestion of 75 grams of glucose. And what you can see in Table S4 is that the change from baseline for Seroquel was not statistically significant at week 24 compared to baseline, while the change from baseline from both olanzapine and risperidone was statistically significant.

So in terms of the area under the curve of the glucose tolerance test, both olanzapine and risperidone showed a statistically significant worsening, whereas quetiapine did not.

Also in Table S5 when you compare the change from baseline in the area under the curve, the difference between quetiapine and olanzapine was statistically significant, obviously olanzapine was worse, and the

Page 1032

olanzapine-quetiapine difference was statistically significant in favor of quetiapine. The difference between quetiapine and risperidone was not statistically significant.

Q. At week 24, can you tell if there was a -- what sort of increase, if any, there was from baseline and fasting glucose for people who were using quetiapine?

A. We have to go -- it's not here. That -- the answer to that question I don't think is in the summary. I'm going to have to go into the body of the document to find that.

MR. McCONNELL: Go off the record for a second.

VIDEOGRAPHER: Off the record at 2:41.

- - -

(A recess was taken from 2:41 p.m. to 2:52 p.m.)

- - -

VIDEOGRAPHER: The beginning

Page 1033

of tape number four. We're back on the record at 2:52.

BY MR. McCONNELL:

Q. Doctor, did you manage to find the fasting glucose results for Seroquel?

A. Yes.

Q. What were the results?

A. The change from base --

MR. PIRTLE: Could you point me to the page? It's a big document.

THE WITNESS: Page 156. The change at week 24 in the quetiapine group was .177 millimeters per liter.

BY MR. McCONNELL:

Q. In the context of all the results of trial 125, did you find the results reassuring or not in terms of whether there was a connection between Seroquel and glucose dysregulation?

A. We found it very reassuring.

Q. Why is that?

Page 1034

A. Because the change in the area under the curve, which is the primary assessment, was not -- did not change significantly between baseline in week 24, and also because there was no change at all in the two-hour value, that is the blood glucose value two hours after glucose challenge showed no change. That value typically begins to go up as diabetes emerges. And the fact that there was no change in that value after 24 weeks on Seroquel was also reassuring.

Q. Doctor, I want to direct your attention to other studies now, studies 126 and 127. My first question to you is, did AstraZeneca collect fasting glucose samples in trials 126 and 127?

A. We attempted to and we also -- and we collected the time since the last meal, which will enable us to ascertain whether -- reasonably ascertain whether the sample was fasted or not.

Q. Can you explain to the jury

Page 1035

what it was that was studied in trials 126 and 127?
A. Trials 126 and 127 were designed to show that Seroquel could prevent relapse in patients with bipolar disorder. It was a complicated trial insofar as we studied patients who either -- had recently had or were having either a manic episode or an episode of depression and who had recovered on Seroquel and the mood stabilizer. And then we randomly assigned patients to continue on the combination or on the mood stabilizer alone. It was a -- it took a long time to recruit the number of patients. And it was a long time to accumulate the number of relapses. And we conducted that study twice in order to be sure of the result.
Q. What was the primary endpoint of 126 and 127?
A. The primary endpoint was relapse of -- having a relapse of either a manic episode or a depressed episode.

Page 1036

Q. Were trials 126 and 127 designed to determine if Seroquel can cause hyperglycemia?
A. No.
Q. Nevertheless, did AstraZeneca collect fasting glucose samples from the patients to monitor the glucose issues?
A. Yes.
Q. What were the efficacy results of trials 126 and 127?
A. Both 126 and 127 were robustly positive showing the decrease in relapse rates to both manic events and depressive events.
Q. Has AstraZeneca submitted the results of trials 126 and 127 to the FDA?
A. We submitted to the FDA and the indication was approved about two weeks ago.
Q. Prior to the submission of the results of 126 and 127 to the FDA, did there come a time when you analyzed

Page 1037

the glucose results from those studies?
A. Yes.
Q. Did you, in fact, do an extensive reanalysis of the results?
A. We did extensive additional analyses of the results of the glucose parameters.
Q. And why did you do that extensive reanalysis?
A. What we found in the pooled safety results was changes in blood glucose of similar magnitude that we had observed before. We also saw similar changes in hemoglobin A1c of the magnitude we had seen before. But in this trial, there were seven reports, seven adverse event reports of diabetes, six of which occurred in the Seroquel patients and only one occurred in the placebo patients. And that could have been a matter of chance, but we wanted to investigate whether or not there was a relationship between Seroquel and the emergence of diabetes. And we undertook

Page 1038

an extensive analysis of all of the data in that trial.
Q. Did that extensive reanalysis involve endocrinologists employed by AstraZeneca?
A. Yes.
Q. Did that reanalysis involve an endocrinologist who is not employed by AstraZeneca?
A. After extensive review and discussion internally, we presented the results to an external endocrinologist.
Q. And after an external discussion and after getting the results from the endocrinologist, was there a consensus among the SERM team about what the data revealed?
A. There was consensus among the clinical team that we took to SERM and we -- the data showed that there was an increase in the -- of about twofold in the rate of emergent hyperglycemia in patients who took Seroquel and a mood stabilizer compared to those that took a

EXHIBIT 12

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE:
SEROQUEL LITIGATION : MDL NO. 1769
:
THIS DOCUMENT RELATES:
TO ALL ACTIONS :

- - -

June 18, 2008

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of BARRY DAVID CHARLES ARNOLD, held at the Radisson Edwardian Manchester, Free Trade Hall, Peter Street, Manchester, England commencing at 9:14 a.m. before Linda L. Golkow, Registered Diplomate Reporter, Certified Shorthand Reporter.

- - -

Golkow Technologies, Inc.
877.370.3377 ph|917.591.5672 fax
deps@golkow.com

Page 362

Q. Is that a common symptom in people with diabetes?
A. It's actually a sign rather than a symptom, but it may be a sign of diabetes mellitus. But, of course, there are many other causes of ketonuria as well.
Q. Do you see where it says, "Seroquel discontinued about 3 months later. DM" or diabetes mellitus "reported to have resolved that same day." Do you see that?
A. Yes, I do.
Q. So, would that be an example of a positive dechallenge?
A. I would regard that as an example of a possible positive dechallenge. The data that's presented in front of me is not full. What we don't know is what concomitant medications the patient was on, we don't know whether those medications were stopped at the same time, and then, equally, what we don't know is, was the

Page 363

patient subject to some sort of dietary control at the same time as discontinuing Seroquel. So, this is a case that lacks complete data, and, therefore, it may appear as a positive dechallenge, but that has yet to be confirmed.
Q. Well, from the data that is presented, does this appear to be a case of positive dechallenge?
A. Well, the important thing is when you are --
MR. BROWN: Objection.
THE WITNESS: The important thing is when you're assessing individual clinical cases like this is that you assess them on the basis of a complete dataset if you're trying to categorize them in the manner that you seem to be attempting.
BY MR. BLIZZARD:
Q. Do you know what efforts were made by the company to get a complete dataset after analyzing this

Page 364

information here?
A. I do not know the specific details of the followup of this particular patient. I'm aware that the company has a standard operating procedure for followup. And to my experience, the data handling teams and the clinical teams who were managing adverse event reports follow that SOP very diligently.
Q. Would the fact that it resolved on the same day give you a clue that it might be a positive dechallenge?
MR. BROWN: Objection to the form.
BY MR. BLIZZARD:
Q. Would that be a pretty strong indication of a positive dechallenge, resolving on the same day that Seroquel was discontinued?
MR. BROWN: Objection.
THE WITNESS: The fact that it resolved on the same day may be taken as an indicator that it

Page 365

might be a positive dechallenge. I would not characterize it as being a clue, and I certainly wouldn't characterize it as being a strong indicator, as you suggest, due to the lack of data.
BY MR. BLIZZARD:
Q. If you look at the one that's second from the bottom of the first page, which is 2004UW06024, it's described as a nonserious event. Do you see this involved an 11-year-old male?
A. Yes.
Q. The dose was unknown, approximately six months, correct?
A. That's correct.
Q. And in the comments, does it say the preferred term was "blood glucose increased"?
A. So, that would be the reported event, yes.
Q. Then it said, "Patient" has arrow up or that would be increased "blood sugar," right?

Page 366

A. That is correct.
Q. And then "TX" -- that's treatment, isn't it?
A. That would stand for treatment.
Q. It says, "equals oral anti-diabetic med (unspecified). Seroquel discontinued. BS normalized," "BS" being blood sugar, correct?
A. That's correct.
Q. So, again, after Seroquel was discontinued, blood sugar normalized, correct?
A. It states that blood sugar was normalized. It implies that it was after Seroquel was discontinued. It doesn't state that factually, whereas the first patient that you indicated to me was very factual, reported to resolve that same day.
Q. Well, it says "Seroquel discontinued," and then the next sentence says "BS" or blood sugar "normalized," right?

Page 367

A. Yes. I'm just being very precise because you tried to use the word "then." That's an assumption or an implication.
Q. Okay.
So, when you're reading this, the blood sugar did not normalize after the Seroquel was discontinued?
A. No. I think it's an assumption that it normalized after discontinuation of Seroquel, but that's not -- should not be stated as a matter of fact, based upon the summary that's provided in this comments column.
Q. Well, we could look at the original adverse event report, couldn't we?
A. Yes, we could, and that perhaps might be more informative.
Q. And do you really think that it was normalized before Seroquel was discontinued?
A. I'm just dealing with facts for the purpose of this jury. I think

Page 368

that you've made an assumption that it's normalized afterwards. I'm not saying that that's not a reasonable assumption. I'm just saying it's an assumption, rather than a statement of fact.
Q. Well, let's go to the next one then. See, this is 2004UW08948. This is a 7-year-old male, correct?
A. It appears that way, yes.
Q. This is a 7-year-old male taking 300 milligrams daily, correct?
A. Yes.
Q. It says the PTs is "Hypoglycemia, Hyperglycemia, Lipids increased," right?
A. That's correct.
Q. It then says, "Patient had decreased blood sugars and increased blood sugars"?
A. Yes.
Q. "BS fluctuating from 42 (fasting) to 202 (1 hour after fruit), HbA1c equals 4.9%, GTT equals 99 (2 hours post glucose). Patient also had

Page 369

increased lipids (no lab data). Seroquel discontinued within one week positive blood sugars back to normal."
Do you see that?
A. Yes.
Q. Is that a case of a positive dechallenge?
A. It's an apparent case of positive dechallenge, but I'm not sure what it's a positive dechallenge to, because it says blood sugar back to normal, but we don't know whether that's referring to the decreased blood sugar, hypoglycemia, or the increased blood sugar, hyperglycemia.
I'd also remark that the HbA1c of 4.9 percent, to my knowledge, that does not equate with a HbA1c level that matches hyperglycemia. Patients who are hyperglycemic who may be tending towards diabetes, you would expect a higher HbA1c than that. So, yes, it appears to be a positive dechallenge, but I'm not sure what event is actually being

EXHIBIT 13

INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT

Tel No: 01625 517679

To: See Below

From: Richard Lawrence

Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

Richard

Distribution:

To:	Don Stribling	(STRIBLING D@A1@APVXC1)
CC:	Lisa A. Arvanitis	(ARVANITIS LA@A1@UWP00)
CC:	Don Stribling	(STRIBLING D @ A1 @ APVXC1)
CC:	Richard Lawrence	(LAWRENCE RA @ A1 @ APVXC1)
CC:	Athena M. Ruhl	(RUHL AM@A1@UWP00)
CC:	Chris R. Griffett	(GRIFFETT CR@A1@UWP00)
CC:	Ricky Bache	(BACHE RA @ A1 @ APVXC1)
CC:	Joher Raniwalla	(RANIWALLA J1 @ A1 @ APVXC1)
CC:	Georgia L. Tugend	(TUGEND GL@A1@UWP00)

EXHIBIT 14

From: Tumas John JA
Sent: 5/11/1999 1:20:48 PM
To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J; Tumas John JA
CC: Goldstein Jeffrey JM
Subject: RE: Small Review

Dear All,

Thank you to those who have commented on this review - I will collate the comments
and pass them on to Dr. Small.Â Dr. Small has contacted Jeff and explained
that the schedule for this review has been moved up.Â We will now have to send
our comments to her tomorrow (Wednesday).Â Therefore, if anyone has any further
comments, please pass them along.

Best regards,

John

From: Â Tumas John JA
Sent: Â Wednesday, May 05, 1999 9:47 AM
To: Â Â Â Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price
Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor
IW; Raniwalla Joher J

Cc: Â Â Â Goldstein Jeffrey JM
Subject: Â Â Â Â Â Â Small Review
Importance: Â Â Â High

Dear All,

Attached is a draft review of quetiapine by Dr. Joyce Small.Â You may recall,
Dr. Small was the lead investigator for Trial 8, high dose, low dose quetiapine
vs placebo.

Dr. Small has asked that we review the document to ensure that the most current
information is included.Â May I ask that comments be limited to this request
and any inaccuracies found.Â She is not looking for editing support and would
like to keep Zeneca's influence on this review minimal.

Please return any comments to me by Thursday, May 13.

Best regards,

John

<<File: QUETIAPI.NE.doc>>

From: Hough Nick NW
Sent: 5/10/1999 9:06:26 AM
To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J; Tumas John JA
CC: Goldstein Jeffrey JM
BCC:
Subject: RE: Small Review

John,

here are my comments on 'Small', some of which reflect my usual concerns, ie selective use of QUEST, overlooking what happened in study 14 etc; however there are also some obvious positive messages that could be added:

* elderly data should be based on 52 weeks if possible
* selective inclusion of QUEST data and not COSTAR means that this paper is unsuitable for 'promotional purposes' - this paper goes even further than the visual aid ('data display' approach?) since the author actually makes a comparative statement - 'with advantages for QTP on depression ratings and the CGI'
* therefore, not 'approvable' for international promotional purposes
* selective inclusion of QUEST data is in conflict with our publication policy since we have no plans to do anything with COSTAR
* study 14, the head to head comparison against haloperidol unfortunately resulted in a 'p-value' in favour of HAL on the positive sympton scale; therefore it is not possible to say that relief of positive symptoms appears comparable to standard neuroleptics
* 1st para under 'neurological effects' tends to switch back and forth between the HAL and CPZ comparative data and doesn't flow logically therefore
* could perhaps include the CLOZ to QTP switch data wrt to weight gain 'reversal'/ improved diabetic symptoms ??
* need medical check on what is said wrt ECG/ QTc intervals
* under therapeutic potential, 2nd para - 'studies of these applications' ...this is written as though something has been described immediately previously relevant to this statement??

Hope this is helpful,

Cheers,

Nick

>----------
>From: Tumas John JA
>Sent: 05 May 1999 14:47
>To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J
>Cc: Goldstein Jeffrey JM
>Subject: Small Review
>Importance: High
>
>Dear All,
>
>Attached is a draft review of quetiapine by Dr. Joyce Small. You may recall, Dr. Small was the lead investigator for Trial 8, high dose, low dose quetiapine vs placebo.

>
>Dr. Small has asked that we review the document to ensure that the most current information is included. May I ask that comments be limited to this request and any inaccuracies found. She is not looking for editing support and would li>ke to keep Zeneca's influence on this review minimal.
>
>Please return any comments to me by Thursday, May 13.
>
>Best regards,
>
>John
>
><<File: QUETIAPI.NE.doc>>
>

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

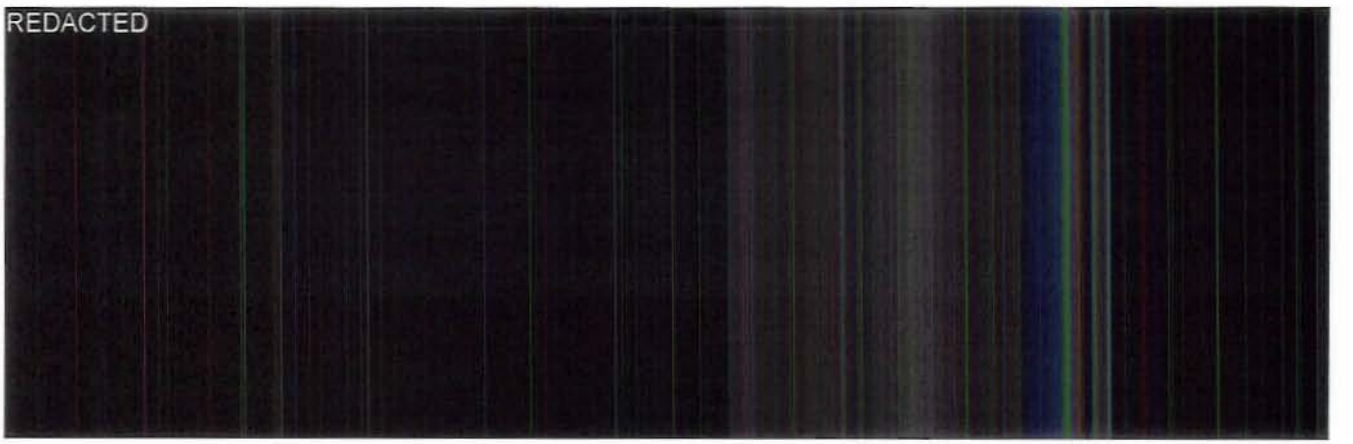
FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL



Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>
Judith Owens
Ext: 24164
11F34 Mereside

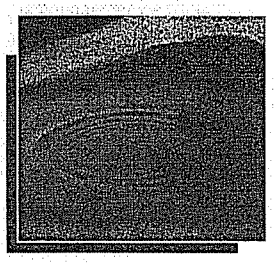
EXHIBIT 15

Managing Weight Gain and Diabetes in Schizophrenia

A Patient Case Study

From the files of
Michael J. Reinstein, MD

Forest Foundation, Inc.
Clinical Research Department
Community Mental Health
Chicago, Illinois



Patient Presentation

- A 49-year-old white male, unemployed, with a long history of psychiatric hospitalizations dating from age 25
- His various diagnoses include acute schizophrenic episode, paranoid schizophrenia, bipolar disorder, and schizoaffective disorder
- The patient also has a history of alcohol abuse

Past Medical/ Psychiatric History

- The patient was first hospitalized in 1976 with religious delusions, auditory hallucinations, and withdrawal
- He was subsequently hospitalized on several different occasions and followed on an outpatient basis after each discharge

Personal History

- There is no family history of psychiatric illness
- The patient was married with a son but has not had contact with either his wife or son for over 20 years
- He has not been gainfully employed for over 15 years
- He lives sporadically with either his mother or in homeless shelters

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. If its signs and symptoms appear, discontinuation should be considered.

Mental/Physical Evaluation

- At presentation, the patient was alert and oriented to time, place, and person, maintained good eye contact, and was stable and in a cooperative mood
- Intelligence appeared to be within normal range
- He denied any hallucinations or ideas of reference
- No EPS, rigidity, or ataxia; no suicidal or homicidal ideations were expressed
- Judgment and reality contact were impaired, he appeared to have no insight, and he frequently laughed inappropriately in response to internal stimuli
- The patient answered questions only after considerable pauses—very briefly and in a low tone and volunteered no information whatsoever
- Physical evaluation revealed a patient overweight by approximately 10 lb

Treatment with SEROQUEL, like other antipsychotics, may result in somnolence, especially during initial dose titration.

Rationale for SEROQUEL Therapy

- Previous treatment with olanzapine 10 mg/day resulted in significant weight gain (10 lb) and subsequent development of type II diabetes (NIDDM)
- Accu-Chek™ was scheduled tid with sliding scale of Humulin® insulin

"This patient demonstrated some classic negative symptoms—blunted affect, emotional withdrawal, poor rapport, lack of spontaneity. Negative symptoms can often be very difficult to treat. We chose SEROQUEL for this patient because in our experience it provides excellent results with negative psychotic symptoms, and weight gain with SEROQUEL hasn't been an issue."

—Michael J. Reinstein, MD

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

Please see accompanying full prescribing information.

SEROQUEL Dosing Regimen

- Olanzapine therapy was discontinued due to weight gain and the development of diabetes
- SEROQUEL was initiated at 150 mg/day for 1 week
- The SEROQUEL dose was then increased to 300 mg/day where it remains

Response to SEROQUEL

- The patient has shown a positive response to SEROQUEL, becoming more spontaneous, more interested in his surroundings, and has demonstrated improved interactions with others
- Blood glucose levels were brought under control, permitting the substitution of an oral hypoglycemic agent for insulin treatments
- Metabolic stability was maintained, allowing the patient to discontinue the hypoglycemic agent and return to a normal diet
- Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on olanzapine

"Our laboratory data revealed a normalization of serum glucose levels which is valid proof of improvement of diabetes and metabolic stabilization. His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also relieved that he no longer has to take daily insulin injections."

—Michael J. Reinstein, MD

Follow Up

- After 7 months, the patient remains well on SEROQUEL 300 mg/day
- The patient is currently taking part in a research study, where he perceives himself as a partner in a joint endeavor. He has achieved clinical improvement and a better quality of life
- He denies having any side effects and is considered competent to handle his own funds and supervised self-medication

"We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications."

—Michael J. Reinstein, MD

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported, and prescribing should be consistent with the need to minimize the risk.

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets
For a more normal life

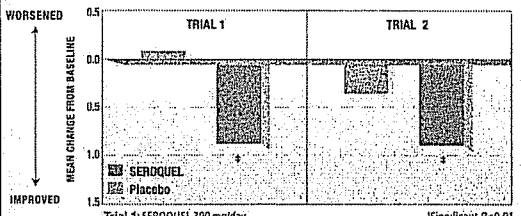
Please see accompanying full prescribing information.

The Strength to Control Both Positive and Negative Symptoms

Across well-controlled trials

Consistent Efficacy in the Treatment of Positive Symptoms[1-4†]

Mean Change in BPRS* Positive Symptom Cluster Scores (LOCF)[1-4†]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)
†Significant $P<0.01$

- **SEROQUEL significantly reduced positive symptom scores**

SEROQUEL was compared with placebo in the following well-controlled, 6-week, acute-phase, multicenter trials.

Trial 1: fixed doses of 75, 150, 300, 600, and 750 mg/day of SEROQUEL (n=255), placebo (n=51).

Trial 2: titrated doses up to 250 mg/day (low dose, n=94) and up to 750 mg/day (high dose, n=96) of SEROQUEL, placebo (n=96).

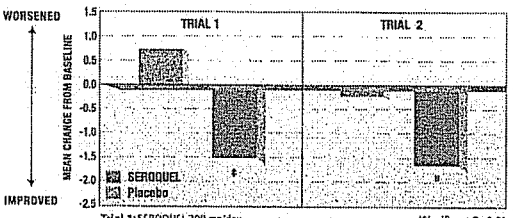
*BPRS: Brief Psychiatric Rating Scale is a clinical assessment tool that measures a combination of 18 individual positive, negative, and general symptom items. The BPRS positive symptom cluster score is the mean of 4 of the 18 individual symptom items for the clinical assessment of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

†LOCF: Last Observation Carried Forward.

Precautions listed in the label include orthostatic hypotension and the risk of cataract development.

...and Consistent Efficacy in the Treatment of Negative Symptoms[1-4†]

Mean Change in SANS‡ Summary Scores (LOCF)[1-4]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)
†Significant $P<0.01$
*Significant $P=0.02$

- **SEROQUEL significantly reduced negative symptom scores**

‡SANS: Modified Scale for the Assessment of Negative Symptoms is used to assess the negative symptoms associated with schizophrenia. The SANS summary score is a total of 5 global items: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention.

The most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

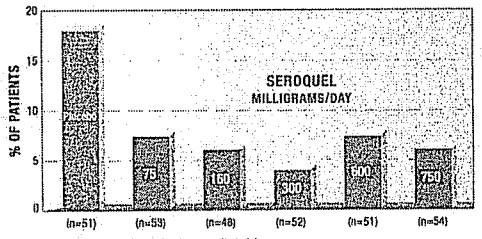
Please see accompanying full prescribing information.

AZSER10427477

Outstanding Overall Tolerability Across the Entire Dose Range

Across the entire dose range,* an EPS† profile no different from placebo

EPS Adverse Events by Dose[1‡]

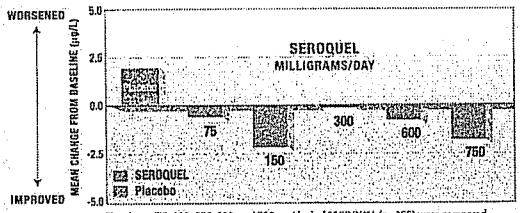


*In a 6-week, acute-phase, placebo-controlled trial.
†EPS: Extrapyramidal Symptoms were defined as dystonia, akathisia, and parkinsonism.
‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- No dose-related EPS were associated with treatment with SEROQUEL® (quetiapine fumarate)[5]

Across the entire dose range, plasma prolactin levels no different from placebo[1]

Mean Change in Plasma Prolactin Levels[1]



Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- There were no statistically significant differences in plasma prolactin levels between any group taking SEROQUEL and the placebo group[1]

Minimal Weight Gain

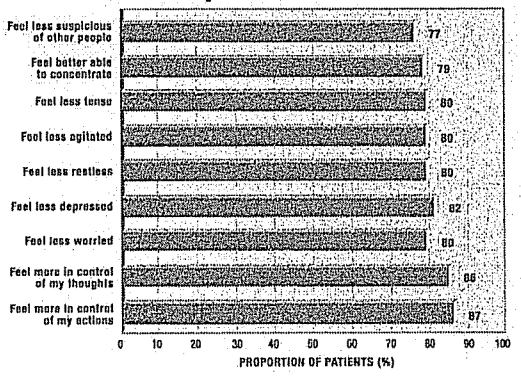
- In a recent open-label study, only 2.5% of patients treated with SEROQUEL (n=553) reported weight gain[6]

Patient Preferred

In a survey of patients (n=129) using SEROQUEL[7]

- 97% reported that they preferred SEROQUEL to previous medications
  - —Two reasons for preferring SEROQUEL were efficacy (29%) and tolerability (41%)[7]
- Benefits noticed in the last 6 months by patients using SEROQUEL

Efficacy-Related Benefits[7]



As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in all placebo-controlled clinical trials, weight gain was approximately 5 lb, which occurred mainly during the early weeks of treatment.[5]

Please see accompanying full prescribing information.

EXHIBIT 16

Clin Drug Invest 1999 Aug; 18 (2): 99-104
1173-2563/99/0008-0099/$03.00/0

Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control

Preliminary Findings

Michael J. Reinstein, Larissa A. Sirotovskaya, Lynne E. Jones, Sangarapillai Mohan and *Maxim A. Chasanov*

Clinical Research Department, Forest Foundation Inc., Chicago, Illinois, USA

Abstract

Objective: The purpose of this open-label, non-randomised, 10-month, retrospective comparative study was to assess changes in weight and diabetes status for patients initially treated with clozapine who developed diabetes and who were then switched to clozapine-quetiapine combination therapy.

Methods: Sixty-five clinic charts were reviewed. All patients were from long-term care facilities. Bodyweight data were collected for this group of 65 randomly selected schizophrenic patients who were on clozapine initially (200 to 800 mg/day for 6 months) and then had quetiapine ('Seroquel') added to their therapy. Clozapine dosages were reduced as quetiapine was added proportionally: 25% of the clozapine dose was changed to quetiapine, using a ratio of exactly 1mg clozapine to 2mg of quetiapine. The quetiapine dosages ranged from 200 to 800 mg/day. This means that each patient received 6 months of clozapine therapy followed by 10 months of combination treatment with clozapine-quetiapine. Weights were recorded monthly, and diabetes status was also performed for patients who developed the condition during clozapine monotherapy.

Results: Changes in weight and the status of diabetes were determined in patients switched from a 6-month clozapine therapy to the 10-month combination clozapine-quetiapine treatment. All changes were statistically significant ($p < 0.001$). Use of this combination therapy in the management of weight gain and diabetes resulted in a 100% satisfactory response. All 65 patients showed weight loss ranging from 0.22 to 10.5kg (0.5 to 23lb) [mean 1.8kg (3.98lb)] after the first month of combination therapy, and the improvement continued through the study duration (10 months). Marked total weight loss ranged from 0.45 to 18.6kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period. 20% of patients (13 patients) who developed diabetes during the 6-month clozapine monotherapy showed significant improvement of disease status with addition of quetiapine. Compliance with medication was 100% and no significant adverse events were observed. The most common adverse event reported by patients was drowsiness. However, this did not contribute a valid reason for discontinuation of clozapine-quetiapine therapy and could be

corrected by dosage adjustment at any time of the report of this adverse effect by patients.

Conclusion: An unexpected, yet welcome, clinical effect of quetiapine is its apparent propensity to induce weight loss and improve glycaemic control in patients who gain weight and develop diabetes on clozapine therapy. The results of this retrospective study support the safety and tolerability of clozapine-quetiapine combination therapy.

Antipsychotic drugs can cause pronounced weight gain. This phenomenon can be regarded as a pharmacologically-induced adverse event and every effort must be made to prevent or vigorously treat it.[1] Clozapine is an atypical antipsychotic agent considered to have superior efficacy for patients with treatment-resistant psychosis.[2] No other atypical antipsychotic agent has been reported to be as effective as clozapine to date. Nonetheless, long-term administration of clozapine markedly influences eating behaviour and increases bodyweight in humans.

It is well known that weight gain is a serious undesirable effect of clozapine therapy, but the mechanism of clozapine-associated weight gain remains uncertain. Discussing neuroleptic-associated weight gain, Brady[9] noted that the mechanism is likely to be multifactorial. Possibilities include drug effects on serotonergic, anticholinergic and histaminic neurotransmitter systems, in addition to effects on endocrine and metabolic functions.

The complication of weight gain can result in noncompliance and a consequent return of psychotic symptoms.[3] Such an outcome can assume major clinical importance in the management of chronic schizophrenia, where maintenance of psychological and social well-being is dependent on regular administration of antipsychotic drugs.

Moreover, many patients with schizophrenia suffer from obesity,[4-6] which is associated with excessive rates of morbidity and mortality;[7] obesity is well recognised to be associated with an increased risk of morbidity from such conditions as diabetes, cardiovascular disease and locomotor disorders.[8] Particularly in these patients, additional weight gain is to be avoided.

Quetiapine ('Seroquel') is one of the most novel antipsychotic agents developed with the benefit of recent research. Quetiapine is an atypical drug for the treatment of schizophrenia or a related psychotic or schizoaffective disorders. Based on preclinical and recent clinical studies, quetiapine appears to have a pharmacological profile similar to that of clozapine without many of the latter drug's serious adverse effects, including weight gain and the development of diabetes.

The current retrospective study was undertaken to determine whether coadministration of clozapine and quetiapine could prevent the significant adverse effects of weight gain and development of diabetes experienced by schizophrenic patients taking clozapine only.

Patients and Methods

Study Participants

The target population consisted of all schizophrenic patients who were resident in Chicago's long-term care facilities. They were men and women ≥18 years of age who met DSM-IV criteria for schizophrenia and schizoaffective disorder. Those who demonstrated weight gain and/or developed diabetes during 6 months' treatment with clozapine monotherapy were eligible for the study.

Patients were receiving clozapine monotherapy and switched to clozapine-quetiapine. We evaluated changes in weight during clozapine monotherapy and clozapine-quetiapine combination therapy and status of diabetes in those developing it during the clozapine treatment time.

The study protocol and consent forms were

approved by the local institutional review board. Written informed consent was obtained from each participant before the start of the study.

Methods

We employed an open-label, non-randomised design using retrospective chart review to identify patients and obtain data. Bodyweight data were collected for a group of 65 randomly selected schizophrenic patients who gained weight, and 13 (20%) of whom developed diabetes, while being treated with clozapine for 6 months and who were then switched to combination clozapine-quetiapine therapy. Clozapine dosages were 200 to 800mg per day. Clozapine was tapered up to 25% of the current dose and quetiapine was added proportionally: 1mg clozapine was substituted for 2mg of quetiapine. The quetiapine daily dosages ranged from 200 to 800mg.

Weight was recorded at baseline, monthly and at the conclusion of the study. Each patient was weighed monthly during the last 10 months of combination clozapine-quetiapine therapy and patients' diabetes status was determined concurrently by recording monthly blood glucose levels.

During the period of clozapine monotherapy, results of routine chemistry examinations revealed marked hyperglycaemia for the 13 patients (20%) who developed diabetes. Serum glucose levels were noted to be 0.36 to 0.85 mg/L, with a mean of 0.675 mg/L. Long-term control of hyperglycaemia was assessed by measuring glycosylated haemoglobin (HBA_{1c}) in fasting patients. Levels of HBA_{1c} were significantly higher than normal for patients who developed diabetes during clozapine monotherapy.

The onset of a response to clozapine-quetiapine combination therapy was defined as the initial appearance of clinical improvement with regard to significant weight loss and noticeable improvement of diabetes status.

Each of the 13 patients with diabetes began a regimen of regular insulin and a diabetic diet. Three patients discontinued hypoglycaemic agents and were placed on a regular diet. During the first 5 to 6 months of combination clozapine-quetiapine therapy, insulin requirements decreased and insulin was later discontinued. A regimen of the oral hypoglycaemic drug glibenclamide (glyburide) at 3 to 4 mg/day was started. Patients who showed a rapid resolution of all symptoms were placed on a regular diet.

Our primary goal was to show significant weight loss during the combination therapy. The second aim was to show that diabetes status could be improved during the combined clozapine-quetiapine therapy.

Statistical Analyses

Statistical analyses were performed on data from the intent-to-treat population, which comprised all 65 patients given the study medication. The statistical significance of improvement from baseline in both weight gain ($p < 0.001$) and effect on blood glucose levels ($p < 0.0001$) was calculated by paired t-tests. Patients were monitored monthly for a response to treatment and adverse effects. Data from all those who reported adverse events as well as improvement in the primary targeted symptom (weight loss and improvement of diabetes during this time) were tabulated in medical records.

Results

All 65 patients (100%) who commenced taking combination clozapine-quetiapine therapy showed significant weight loss and improvement in diabetes status during the period of combined clozapine-quetiapine therapy.

Weight Loss

At baseline, weight ranged from 59.5 to 125kg (131 to 275lb) [mean 104kg (229.2lb)]. During clozapine monotherapy, across all patients, the mean weight gain was 6.5kg (14.3lb; 6.25%) for the period of 6 months.

Marked changes in bodyweight were observed when patients started treatment with clozapine-quetiapine combination therapy. The quetiapine

dose at 1 month ranged from 200 to 800mg per day. The individual weight loss ranged from a minimum of 0.23kg (0.5lb) after the first month of treatment to a maximum of 18.6kg (41lb) at the conclusion of the study [mean 9.4kg (20.75lb)].

All the changes in bodyweight were statistically significant ($p < 0.001$). All 65 patients showed weight loss ranging from 0.23 to 10.5kg (0.5 to 23lb), with a mean loss of 1.8kg (3.98lb), after the first month of combination therapy. Subsequent monthly losses were 1.8kg (3.98lb), 1.796kg (3.96lb), 1.456kg (3.21lb), 1.12kg (2.47lb), 0.966kg (2.13lb), 0.68kg (1.50lb) 0.635kg (1.40lb), 0.408kg (0.90lb), 0.318kg (0.70lb) and 0.227kg (0.50lb).

The improvement continued throughout the study to the end-point (10 months). Marked total weight loss ranged from 0.45 to 18.61kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period.

Diabetic Status

Twenty percent of the 13 patients who developed diabetes during clozapine monotherapy showed significant clinical and laboratory improvement of diabetes while taking clozapine-quetiapine. Weight gain in this group of patients ranged from 3.2 to 24.1kg (7 to 53lb) [mean 8.5kg (18.69lb)] during clozapine therapy. Thirteen patients who developed diabetes due to clozapine showed significant weight loss, with a mean loss of 1.75kg (3.84lb) after the first month of combination treatment and 4.68kg (10.3lb) at the conclusion of the study.

During clozapine therapy, patients showed significant increases of up to 10 to 15% in the HBA_{1c} level (monthly mean increase = 1.34%). HBA_{1c} levels returned to normal (<7%) at the end of the study (monthly mean decrease = 0.78%): results of routine chemistry examinations at the end of the 10-month treatment period revealed normalisation of blood glucose levels, resulting in a rapid decrease in insulin requirements and/or discontinuation of insulin treatment and starting of a regimen of an oral hypoglycaemic agent. Three patients who discontinued hypoglycaemic agents were placed on a regular diet and remained metabolically stable.

Positive results were assessed in terms of normalisation of blood glucose levels, discontinuation of insulin therapy, switch of patients to oral hypoglycaemic drug and placement of patients on a regular diet. According to our data, results of a laboratory examination revealed a normalisation of serum glucose levels in three of our patients, which is valid proof of improvement of diabetes and metabolic stabilisation.

Overall, our data demonstrated that no adverse behavioural changes occurred during the 10-month study period. No patients stopped therapy because of drowsiness; this was corrected by adjusting the dose. Compliance with medication was 100% and no significant adverse events were observed.

Discussion

The multiple clinical studies and reports from different researchers demonstrate significant weight gain in a group of schizophrenic patients during clozapine treatment. In spite of the considerable efficacy of clozapine, increased appetite, craving for sweets and weight gain are commonly cited by patients as their primary reason for discontinuation of the treatment.

The mechanism of clozapine-associated weight gain remains uncertain, as does the cause of hyperglycaemia associated with high doses of clozapine.

The first report of severe insulin-dependent hyperglycaemia precipitated by clozapine therapy in a patient with a previously unremarkable medical history was introduced by Kamran et al. in 1994.[10] According to his report, the sustained hyperglycaemia, which required insulin therapy and diet modification, completely resolved following discontinuation of clozapine, but he continued 'we do not know whether clozapine alone or the combination of clozapine, benztropine, and ranitidine was responsible for the hyperglycaemia'.[10]

The majority of patients in our current study were on valproate semisodium (divalproex sodium). Thus, the possibility that drug combinations

may have affected the metabolism of one or more agents, resulting in altered drug levels and impaired glucose metabolism, must be kept in mind.

Diabetic ketoacidosis associated with clozapine treatment was also reported by Koval et al.[11] The author described a history of diabetes for a patient who did not have elevated serum glucose levels previously. This patient developed diabetes 6 months after initiation of clozapine treatment and was admitted to an intensive care unit in a comatose condition. She initially required insulin treatment. Clozapine treatment was discontinued slowly, and her insulin requirements decreased and insulin was later discontinued. This case also demonstrates that clozapine may precipitate insulin-dependent diabetes in some individuals. Further studies are necessary to investigate the relationship between clozapine therapy and blood glucose regulation.

Quetiapine is a recently introduced antipsychotic drug. In its pharmacological profile, quetiapine resembles other atypical antipsychotic agents with the exception of possible weight gain. An unusual clinical effect of the drug is its apparent propensity to induce weight loss, which could be a cause of the improvement of diabetes during combination clozapine-quetiapine therapy. There are obvious clinical implications arising from the propensity of an effective antipsychotic drug to produce weight loss as well as cause improvement in, and in some cases resolve, diabetes, leading to discontinuation of insulin or other hypoglycaemic drugs.

A great deal of work remains to be done with quetiapine, in particular to elucidate its mechanism of action and to determine the optimal dosage and length of treatment in combination with clozapine.

The current retrospective analysis was done to determine whether coadministration of clozapine and quetiapine could attenuate the significant unpredictable adverse effects of weight gain and development of diabetes during clozapine monotherapy.

This study may contribute to the discovery of novel therapeutic approaches to the treatment of refractory schizophrenic patients with clozapine and quetiapine without serious adverse effects such as significant weight gain and development of diabetes, which can occur during clozapine monotherapy.

To date, no study had compared clozapine monotherapy and combination clozapine-quetiapine therapy. Future studies should focus on larger sample sizes to corroborate the findings of the current study. Furthermore, a double-blind, randomised, prospective study would have been preferable. Limitations of this current retrospective analysis are non-standardised administration, uncontrolled concomitant therapy, non-randomised assignment and data censoring.

Conclusion

The current study demonstrated that the combination of clozapine and quetiapine had a significant, positive effect on weight and glycaemic control.

Acknowledgements

This study was supported by a grant from Zeneca Pharmaceuticals Inc., Delaware, USA. 'Seroquel' is a trademark, the property of Zeneca Pharmaceuticals Limited.

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Correspondence and reprints: Dr *Michael J. Reinstein*, Forest Foundation Inc. Clinical Research Department, 4755 North Kenmore Ave., Chicago, IL 60640, USA.

EXHIBIT 17

From: Beamish, Don G
Sent: Monday, November 05, 2001 10:24 PM
To: Pusey, James M
Cc: Tugend, Georgia L
Subject: FW: Reinstein Response Letter and Backgrounder

Importance: High

Attachments: Reinstein Response.doc; Reinstein Backgrounder.doc
James,

Georgia has spoken to Dr. Reinstein directly and has drafted the attached response to his letter. Georgia has also provided some background information that would not be sent to Dr. Reinstein. I would recommend that the letter should be sent from Georgia. I think it is important for Georgia to maintain her relationship with Dr. Reinstein and be viewed as his key contact. As I suggested in my previous memo, I also think it would be appropriate for me or someone else in a leadership role to acknowledge his concerns directly either in a phone call or in a follow up letter. Please let me know how you would like to proceed.

Don

-----Original Message-----
From: Tugend, Georgia L
Sent: Monday, November 05, 2001 4:49 PM
To: Beamish, Don G
Subject: Reinstein Response Letter and Backgrounder
Importance: High

November 5, 2001

Michael J. Reinstein MD, PC
Community Mental Health Services
4755 North Kenmore
Chicago, IL 60640

Dear Dr. Reinstein,

I am in receipt of your in your letter dated October 23, 2001 to David Brennan. and hope to address the points you raise.

Here at AstraZeneca we are aware of the critical nature of our relationship with you and your colleagues that has been established with individuals from our Sales, Marketing, and Medical functions. We value the contribution that you, as an important customer, have made toward the success of SEROQUEL and appreciate your candid feedback to us.

Regarding your first point, there is little doubt that Janssen has funded more research in support of risperidone in the past than AstraZeneca did for SEROQUEL. This, while not ideal for us, is not surprising given that risperidone was launched nearly 4 years before SEROQUEL and that Janssen does provide significant resources to the #1 drug in their overall business. This has resulted in a rich research portfolio to date. However, like you, we recognize the excellent attributes and benefits of SEROQUEL and with its current level of success and its promise for even greater market penetration, the company has increased resources in support of its clinical development program and commercial activities so that past trends may well reverse

There really is no dispute regarding the second point you raise regarding communication of dosing issues. One of the greatest challenges SEROQUEL has faced is ensuring that the appropriate dose in used. The dosing strategy was never to limit use to 300 mg/day but because of trials submitted to the FDA for registration, the Prescribing Information contains the statements "initial target dose of 300-450 mg/day" and dose limit of 800 mg/day for safety. This led to confusion and uncertainty in the minds of some prescribers, which we have aggressively attempted to address in numerous promotional and educational programs over the past several years.

Thank you for bringing the reimbursement issue to our attention. We have confirmed that Omnicare in Chicago is denying claims beyond 800 mg/day of SEROQUEL. They apparently are doing likewise with another atypical antipsychotic. While we will work with our Account Directors and Advocacy Groups to alleviate this situation in the near term, your point to do research to obtain a higher dosing ceiling is well taken.

AstraZeneca prides itself at being a customer-focused organization and as such timely payments of honoraria and reimbursement for expenses is essential. We have put a new system in place for the payment of honoraria but we realize there is room for improvement particularly around travel and other out-of-pocked reimbursements. Likewise an AstraZeneca speaker should not be inconvenienced if a program is cancelled for reasons outside their control and we will address this with our Professional Relations and Sales Departments.

We value the contributions of leaders in Psychiatry such as yourself and appreciate our long-standing relationship with your group. And although we must balance the needs of AstraZeneca products across the entire business portfolio, please let me assure you that the company is in complete support of SEROQUEL and hope to have your continued support as well.

Sincerely,

Background: letter from M. Reinstein, et al to D. Brennan, dated Oct. 23, 2001

This group does generate a very significant amount of SEROQUEL sales for us. They run several clinics in the city of Chicago and by all accounts have over 1,000 patients on SEROQUEL. While likely not "the largest prescribers of SEROQUEL in the world", they probably are in the top 5 in the US.

Because of their patient volume they are attempting to establish themselves as a research center.

This group, in particular John Sonneberg PhD, Director of Research has been extremely persistent in recent months with demanding research from AZ. Their comments to several AZ employees suggest since they use large volumes of SEROQUEL they should by default be doing research on our behalf. They have further implied that should they not get research funding that they would switch patients currently on SEROQUEL to competitive agent(s).

Our Clinical colleagues have significant and numerous issues in past with the quality of research that this group has produced in the past. Matters such as not getting informed consent from study participants, modification of protocols without permission, etc has made the business understandably reluctant to place studies with this group. There is little confidence that Good Clinical Practices can be adhered to. Their research is often criticized by peers in Psychiatry.

However, in attempts to have a "win-win" for all, we have offered funding for projects such as retrospective chart reviews (as opposed to well-controlled, double blinded trials) that could do little harm but still demonstrate commitment to the customer. The group has not accepted this and they continue to insist on funding to do a high dose SEROQUEL trial (>1600 mg/day) that is addressed in Point 2 of their letter.

Drs. Reinstein and Chasnov are prolific speakers on our behalf and are particularly influential with prescribers outside the Chicago regional area. They get numerous speaking engagements because of their own experience and belief in the brand. (Note: they are generally held in poor regard among their peers in the greater Chicago area).

Because of their importance to our business, they have had an extraordinary amount of attention given to them. A number of AZ personnel from numerous functions have had open, honest but collegial, cordial dialog with Drs. Reinstein and Sonneberg. Contact has been with Sales, Marketing, USDD, and Scientific Commercialization at several levels, including Leadership levels within our organization. All involved have had extremely good communication internally and with the customers to address their interests. Every discussion appeared to be well received at that time. However, actions like this letter and other persistent calls demanding research continue to occur despite our attention to their group, thus disappointment with the "time for new leadership" remark.

EXHIBIT 18

DISCUSSION DOCUMENT

SEROQUEL™

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

SERM NO 32 - 22 JUNE 2000 - MINUTES

Participants : M Brecher

After review of the available data SERM considered that no amendment to the CDS was justified

ACTION - WG create a position paper.
MB keep this under review and bring back to SERM the expected additional clinical trial data

AUTHOR(S):

Wayne K. Geller MD
Medical Director, Drug Safety
Wilmington, DE

SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

Presently, the SEROQUEL Core Data Sheet (CDS) does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with SEROQUEL therapy. Safety data derived from clinical trials and spontaneous reports, despite often containing limited information, suggest the possibility of an association between SEROQUEL use and impaired glucose regulation including occasional reports of new onset diabetes mellitus. While none of these reports are absolutely steadfast, the number of reports is fairly sizeable. Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis. While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for SEROQUEL and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for SEROQUEL for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The SEROQUEL core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with SEROQUEL:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The SEROQUEL US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels $\geq$110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

(1) Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or

(2) Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or

(3) Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with
Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:

Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)

- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12 to 16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

(1) The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).

(2) Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases.

Case Number: 2000UW01164

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started SEROQUEL 200 mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on SEROQUEL. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving SEROQUEL, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving SEROQUEL 300 mg daily since 06 December 1999. On 26 January 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. SEROQUEL was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include zoloft, klonopin, haldol and depakote.

Follow-up 23 February 2000: Pharm D reports that "after further testing, the attending physicians did not feel that SEROQUEL was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving SEROQUEL and developed diabetes. Physician feels that SEROQUEL may possibly be responsible for the development of diabetes.

Follow-up 11 November 1999: Physician reports that the 47 year old female (not 45) had been receiving SEROQUEL 600 mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. SEROQUEL was tapered for discontinuation. Concomitant medications include klonopin and benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "SEROQUEL caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS

A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving SEROQUEL 100 mg every evening since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of SEROQUEL was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 September 1999, SEROQUEL dosage was again decreased to 25 mg every evening. The patient had been receiving risperidol prior to

SEROQUEL. Concomitant medications include ritalin for attention disorder and serzone for depression.

Case Number: 1999UW00969

COMPLICATIONS OF DIABETES MELLITUS

A report has been received from a physician concerning a 28 year old male patient who was taking SEROQUEL and lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14 March 1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.

*Follow-up received 22 March 1999: A pharmacist reports that the patient started zithromax on 10 March 1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14 March 1999: The patient presented on 14 March 1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15 March 1999. The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05 May 1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10 to 16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967

DIABETES

A report has been received from a physician concerning a 17 year old male who is receiving SEROQUEL 200 mg twice daily for schizophrenia. The patient was initially started on 100 mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300 mg daily. Patient also receives paxil and depakote. Patient continues on SEROQUEL.

Case Number: 1999UW00288

BLOOD SUGAR RISING

A report has been received from a 58-year-old diabetic female patient who has been receiving SEROQUEL since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 January 1999 the reading was 321.

Case Number: 1999AP06660

LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA

A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving SEROQUEL since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300 to 400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started SEROQUEL in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control, particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5 mg/day. At the time of reporting the events were ongoing.

The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757

DIABETES, KETOACIDOSIS.

A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750 mg daily for psychosis since November 1997. He was receiving acamprosate, depixol and priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.

The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218

DIABETES DURING PREGNANCY

Patient developed diabetes during pregnancy and started insulin on 30 September 1999. Baby due 06 December 1999, but patient's water broke 30 September 1999 and baby born in October 1999. See case 1999AP06076.

Case Number: 1999AP02989

DIABETES MELLITUS

This patient started treatment with SEROQUEL on 13 November 1998 and with fluoxetine on 12 November 1998. Urine and blood tests on 26 November 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985

NON INSULIN DEPENDENT DIABETES

A physician reported that a 44 year male patient was given SEROQUEL 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting SEROQUEL, the patient developed non-insulin dependent diabetes. SEROQUEL was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554

CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.

A report has been received from a physician concerning a 58 year old male patient who received SEROQUEL 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081

HYPERGLYCAEMIA

Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 1998. Open label medication started on 14 September 1998 and ended on 26 September 1998. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844

HYPERGLYCAEMIA, DIABETES.

A report has been received from a physician concerning a male patient in his early forties who has been receiving SEROQUEL for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.

NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken SEROQUEL since July 1998. On 31 August 1998 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 October 1999: Further information reveals that the patient was receiving SEROQUEL 200 mg for a bipolar disorder since July 1998. On 31 August 1999, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. SEROQUEL was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408

HYPERGLYCAEMIA (NON-SERIOUS)

A pharmacist and a nurse reported that a male patient taking SEROQUEL developed hyperlycaemia. The pharmacist considered the event unrelated to SEROQUEL; the nurse considered the event related to SEROQUEL. The patient was also taking stelazine.

Case Number: 1998AP45979

LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR

Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with SEROQUEL, SEROQUEL dosage has been reduced from 400 to 200mg. The physician is thinking of stopping SEROQUEL altogether.

Case Number: 1998AP18089

HYPERGLYCAEMIA.

A report has been received from a physician concerning a 32 year old male patient who has been receiving SEROQUEL from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.

On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803

DIABETIC KETOACIDOSIS

A report has been received from a physician concerning a 36 year old male who has been receiving SEROQUEL in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. SEROQUEL started on 06 September 1996. The patient had recently been diagnosed with diabetes mellitus which was controlled on glucotrol. On 18 March 1997, 28 weeks after starting SEROQUEL, he was admitted to hospital with decreased level of consciousness. He had not been taking his glucotrol or SEROQUEL for 3 to 4 days prior to admission. He was given IV fluids and insulin but later developed severe acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were:

sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin and food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted SEROQUEL. The event resolved on 01 April 1997. The investigator felt that there was not a reasonable possibility that the event was related to SEROQUEL.

Case Number: 1997AP36246

UNCONTROLLED DIABETES

A report has been received from a physician concerning a 29-year old male who has been receiving SEROQUEL since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. SEROQUEL treatment was put on hold and the patients diabetes treated with humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the SEROQUEL therapy.

Case number: 1997AP35710

UNCONTROLLED DIABETES MELLITUS

A report has been received regarding a 45 year old male who has been receiving SEROQUEL as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 August 1997, 163 days after starting SEROQUEL, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.

The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874

PNEUMONIA, DIABETES, HYPERTENSION

This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with SEROQUEL as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.

The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737

DIABETES MELLITUS

This 52 year-old-female with schizophrenia was taking SEROQUEL 400 mg from 28 January 1995 as part of a clinical trial. On 31 January 1995 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April 1995, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.

This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544

AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in SEROQUEL trial on 26 September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4 November, the patient developed

symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with SEROQUEL.

Case Number: 1994AP03286

HYPERGLYCAEMIA

An investigator reported that a 53 year old female patient started taking SEROQUEL on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893

HYPERGLYCAEMIA

An investigator reported that a 45 year old male was treated with SEROQUEL beginning on 4 March 1994. Concomitant medications included zantac and haldol. The patient had no history of diabetes mellitus. He had recently stopped taking an unblinded SEROQUEL study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. SEROQUEL was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5. DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of pre-existing diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of pre-existing diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to SEROQUEL.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily SEROQUEL dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months

(median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily SEROQUEL dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to 21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking SEROQUEL 150 mg daily for 30 months. The latter report contains scant information, except the daily SEROQUEL dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient

developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

6 REFERENCES

(1) Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

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(3) Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

(4) Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

EXHIBIT 19

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL	:	CASE NO.
PRODUCTS LIABILITY	:	
LITIGATION	:	6:06-md-01769-ACC-DAB
	:	
MDL Docket No. 1769:		

- - -

May 7, 2008

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of WAYNE K. GELLER, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania 19103, commencing at 9:00 a.m., on the above date, before Linda Rossi Rios, RPR, CCR and Notary Public.

- - -

Golkow Technologies, Inc.
One Liberty Place, 51st Floor
1650 Market Street
Philadelphia, Pennsylvania 19103
877.370.3377

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Dorothee Wientjens...," I'm sure I'm mispronouncing that, "...to respond to the Dutch Authorities regarding quetiapine and glucose metabolism." Did I read that correctly?

A. Yes.

Q. So you knew that the information you were giving to Ms. Wientjens, if I'm pronouncing that correctly, was going to be turned over to the Dutch authorities. Right?

A. I was under the impression that it would be. However, I was responding to her request.

Q. And you understood that her request was for information she could turn over to the Dutch authorities. Right?

A. Well, again, I know that there was a request that came from Dorothee Wientjens, I believe is the way she pronounces her name, and I don't have that e-mail in front of me to answer your question with the accuracy that I would

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like to.

Q. All right, sir. And then you said, "I sent Dorothee a copy of the recent Seroquel Safety Position Paper on DM and related disorders." True? That's what you said?

A. Yes. And, again, I was referring to the document which was termed a position paper, which had -- was unofficial and, in fact, was not a position paper on this topic.

MR. ALLEN: Sir, object to that as nonresponsive.

BY MR. ALLEN:

Q. You refer to it as a "Seroquel Safety Position Paper on DM and related disorders." Right?

A. Again, to make sure that we're taking this in the right -- in the correct context, this so-called Seroquel safety position paper, as it was titled, was not, in fact, an official company document and did not reflect our view and our knowledge of diabetes at that time,

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sir.

MR. ALLEN: Okay. Object to that as nonresponsive.

BY MR. ALLEN:

Q. And then you go on and you apologize. What are you apologizing for, sir?

A. Well, being relatively new to the company, it occurred to me, right afterwards it was brought to my attention that Ms. Wientjens' request appropriately should have gone through the global regulatory affairs director who then should have contacted myself and others in order to respond to the Dutch regulatory agency.

Q. So you made a mistake by letting the safety position paper go out to the regulatory authorities?

MR. RABER: Objection to form.

BY MR. ALLEN:

Q. Sir?

A. I made a mistake by

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submitting a document which was not correct, number one. And number two, I did so through an individual that was someone who I should not have given the document directly to.

Q. Who -- what department did Dorothee work in?

A. I don't know.

Q. Who was she?

A. I don't know.

Q. Okay. But Exhibit 17 is a document that you believe, at least you believe this is one of the documents that the Dutch authorities received in advertently. Is that correct?

A. I believe this is the document.

Q. You believe it is this document. Thank you, sir.

We got this from y'all's files and you authored Exhibit 17, did you not?

A. Yes, I did.

Q. And do you agree with the

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fact that based upon your review of the information you had available, if you look on page 11, the last page, do you agree --
A. I'm sorry, 11 out of --
Q. Yes, sir, I see that. It's the last page. Are you at the last page?
A. Yes.
Q. Do you agree with the statement that you drafted, "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals." Do you agree with that statement?
A. No, I disagree with that statement, sir.
Q. Okay. Why did you write it?
A. That statement was an artifact of an earlier discussion document which was a draft discussion document for the June 2000 SERM, and did

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not reflect my view of diabetes at the time that I presented at SERM in June of 2000.
Q. Well, in fact -- so you were the presenter at SERM in June of 2000?
A. Yes, I said that previously.
Q. Was Dr. Brecher there?
A. He was on the telephone, I believe.
Q. Did you in June of 2000 as presenter specifically state that Seroquel may cause impaired glucose regulation in some individuals? Isn't that what you did at that meeting?
MR. RABER: Object to the form.
BY MR. ALLEN:
Q. Isn't that what you said?
A. I think to be absolutely correct, I need to see a copy of the discussion document that was circulated for the June 2000 SERM.
Q. Now, when did you prepare Exhibit 17, sir? After the SERM meeting,

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isn't it, in June of 2000 you prepared this?
A. Exhibit 17 would have been prepared sometime in the fall of 2000, I believe.
Q. If the database that we have that was given to us in the production says this document was dated August the 10th, 2000, does that sound about right to you?
A. No, it doesn't.
Q. Can you give me or the jury any help by telling us why that database which we were provided which said August the 10th, 2000, is incorrect?
MR. RABER: Object to the form.
THE WITNESS: It certainly would not have coincided with the request on the MEB. However, I failed to consider the possibility that I started to prepare a position paper after the June SERM that discussed the issue of

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diabetes mellitus and Seroquel therapy. And, in fact, I recall specifically using as a template a draft discussion document which contained the same language that you just read, sir.
BY MR. ALLEN:
Q. And by the way, sir, that's not a true statement, that there are no reports of positive dechallenges, that's just not a true statement, is it?
MR. RABER: Objection to form.
BY MR. ALLEN:
Q. There's positive dechallenges throughout the adverse experience database in regard to Seroquel and diabetes and hyperglycemia, aren't there, sir?
MR. RABER: Objection to form.
THE WITNESS: I can state that when the discussion document was prepared, which would have

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been in May, roughly May of 2000, that that statement was correct and accurate.
BY MR. ALLEN:
Q. You also on that same -- at or about that same time, prepared -- following the June 2000 SERM meeting, you prepared Exhibit 18, the justification --
MR. RABER: Hang on. You said we were going to do one more document --
MR. ALLEN: Right.
MR. RABER: -- and we were going break.
MR. ALLEN: Yes, sir. And I'm wrong because based upon his answer, there's one more question I want to ask about Exhibit 18.
MR. RABER: I just want to know when we're going to break?
MR. ALLEN: And I told you my best --
MR. RABER: You told me and you told me wrong.

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MR. ALLEN: I was mistaken. I did not know the witness' answer. And I'm showing him Exhibit 18. I'm not trying to cause any trouble. And I'd ask him to look at Exhibit 18, which is a justification document that he also prepared concerning reasonable evidence and then we will be done.
- - -
(Exhibit Geller-18, Justification Document, was marked for identification.)
- - -
BY MR. ALLEN:
Q. Sir, I'm handing you what's been marked as Exhibit 18, which is another document from the database that you said was prepared by you on or about August the 10th, 2000. Did you prepare this justification document on Seroquel and weight gain?
A. I am listed as the author in

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the document. However, I wish to point out that this document, too, is a draft document.
MR. ALLEN: Yes, sir.
Object to that as nonresponsive.
BY MR. ALLEN:
Q. Sir, did you prepare Exhibit Number 18?
A. My name is listed as the author on this document, and I recognize the fact that it is a draft that I prepared.
Q. Yes, sir. Okay. And by the way, did you review Exhibit 17 in preparation for your deposition?
A. Yes.
Q. And you've already testified you reviewed Exhibit 16 in preparation for your deposition, or not, I can't recall, to be honest with you?
A. Yes, I believe so.
Q. Did you -- have you reviewed Exhibit 18 in preparation for your deposition? The justification document

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on Seroquel and weight gain.
A. I don't believe I have.
Q. Okay. Now, you've already testified earlier today any documents you reviewed in preparation for your deposition in this -- these 15 or 20 volumes occurred during the time you were meeting with counsel. Right?
A. Yes.
Q. You never reviewed these documents outside of the presence of counsel. Correct?
A. Correct.
Q. Okay. All right, sir. And in the justification document on Seroquel and weight gain you wrote, Exhibit 18, didn't you also state that "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can produce significant weight gain in select individuals. The Seroquel CDS mentioned the possibility of 'limited' weight gain associated with Seroquel

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safety position paper draft prepared by you, and let's -- let me stop here and it's my fault. You started working in the safety surveillance department of AstraZeneca in May of 2000. Is that correct?

A. Actually in April.

Q. I'm sorry, April. So in other words, your conclusions that we've seen in regard to weight gain, you were able to reach those conclusions between the time you started working in April and by the time you prepared the document. True?

A. The document was prepared in -- for the June SERM, which meant that that data was looked at between my join -- in the time between my joining the company and the discussion document.

Q. Thank you, sir. Now, in this Exhibit 17, safety position paper, you state, Safety data derived from clinical trials and spontaneous reports often containing limited information may

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represent a weak signal linking Seroquel with impaired glucose regulations -- regulation, including occasional reports of new onset diabetes mellitus. None of these reports are absolutely steadfast (i.e., there are no clear index cases and there were no reports of positive dechallenges/rechallenges) and most have either incomplete information or other explainable causes. Although the number of reports is fairly sizable, it was felt that there is insufficient evidence at present to warrant an amendment to the Seroquel Core Data Sheet. Did I read that correctly?

A. Yes.

Q. You go on to state, "However, it was agreed that the topic will be kept under ongoing review and will be reassessed at a later time." Did I read that correctly?

A. Yes.

Q. Why did you say the number of reports is fairly sizable?

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A. Well, it was my impression at the time that we conducted our pre-SERM activities, which would have been sometime in May 2000, that relatively speaking, that meeting, looking at a frequency table of all adverse events that had been reported in the postmarketing realm in the serious clinical trial adverse event reports, that compared to, for instance, compared to bone fractures, for instance, that the numbers seem fairly sizable. However, I have to confess that at that particular time, I had no idea how many patients had been exposed to Seroquel. So it was a statement of relative comparison, sir.

Q. Of course, when the document we saw yesterday was prepared to the FDA, you did not tell the FDA, you being AstraZeneca, that you had a fairly sizable number of diabetes cases, did you?

A. We presented all the data that we had from all sources, including

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clinical trial sources, including the literature, including the postmarketing sources that were contained in this particular document. So in answer to your question, I believe we provided them with more than what was provided here.

MR. ALLEN: Objection. Nonresponsive.

BY MR. ALLEN:

Q. You did not tell the FDA that the number of adverse experience reports concerning diabetes mellitus, you did not use the term that they were fairly sizable, did you, sir?

A. Sir, FDA requested the data. We provided them with every piece of data they requested. We provided them with our own analysis. And I have to confess that once I learned what the exposure, meaning how many patients had been exposed to Seroquel, which would have happened sometime between the preparation of the draft discussion document, from which this was based, until the SERM, it

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became apparent to me that the number of cases -- of reported cases of diabetes was not so sizable.
Q. In fact, you not only did not tell the FDA that there was a fairly sizable number of reports, you told the FDA, you being AstraZeneca, that there were very few cases of diabetes mellitus, didn't you?
A. I don't recall that specifically, sir.
Q. If it's reflected in the document that you provided to the FDA, you don't recall reviewing that document in preparation for your deposition?
A. I reviewed the document. I don't have photographic memory unfortunately, sir.
Q. I don't expect you to. And I'm just asking you whether or not -- and no one has a -- well, some people have some photographic memory. Some people do. But do you recall in reading the document that your company submitted to

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the FDA in August of 2000, that your company told the FDA that there were very few cases of diabetes mellitus and hyperglycemia? Do you recall that or not?
A. I don't recall that. However, I know that at the time we submitted the document to FDA, we had exposure figures to put -- to put these number of reports into context.
Q. Do you recall that when your company submitted the document to the MEB in January of 2001, your company told the MEB that there was a relatively small number of postmarketing reports of glucose dysregulation? Do you recall that?
A. I don't recall the specific language, sir.
Q. Nevertheless, you would agree that in the documents you prepared, the safety position paper, Exhibit 17, that you prepared, you said that the number of reports is fairly sizable? Do

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you agree with that?
A. This draft so-called safety position paper does indeed contain that statement, and, again, was written without having any contextual information as far as exposure was concerned.
Q. Now, at the last page of Exhibit 17, the safety position paper that was prepared by you, do you see the final paragraph?
MR. RABER: Object to form.
THE WITNESS: Yes.
BY MR. ALLEN:
Q. And you state, do you not, sir, While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest -- let me start again.
You state in writing, "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes

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mellitus in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet based upon postmarketing and clinical trial safety data." That's your language, is it not, sir?
A. Yes.
Q. Was diabetes -- and do you agree with that statement, by the way, that you wrote?
A. No, I completely disagree with that statement. As I indicated yesterday, this statement was an artifact from a draft discussion document which was not the basis for the June 2000 SERM discussion document. So this was my -- this happened to be the statement which I felt was not factually correct in this document.
Q. Now, did you testify that -- let me come back to that in a minute.
So your testimony at this juncture is that final paragraph Exhibit -- of Exhibit 17, which says that

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Q. That's right.
A. No.
Q. Did you rewrite -- strike that. Let me back up.
I think you said that you used as a template for Exhibit 17 an older draft of a discussion document; is that right?
MR. PIRTLE: Objection, form.
THE WITNESS: Yes, I did.
BY MR. RABER:
Q. And is --
To the best of your knowledge, is Defendant's Exhibit 202 the template that you used when preparing Exhibit 17?
MR. PIRTLE: Objection to form.
THE WITNESS: Yes, it is.
BY MR. RABER:
Q. It appears if you look at Geller Exhibit 17, the one on the right, that you rewrote that summary and

Page 1122

conclusions paragraph; is that right?
A. Yes.
Q. Did you rewrite the last paragraph on Defendant's Exhibit 17 -- I mean Geller Exhibit 17?
A. No. It's exactly the same as the one in Defense Exhibit 202.
Q. When you say you made a mistake, is that the mistake you made, by leaving in that paragraph from this old template?
A. Yes, it is.
Q. Did the paragraph that got left in by mistake accurately reflect what had happened at the SERM meeting in June of 2000?
MR. PIRTLE: Objection to the form.
THE WITNESS: No, absolutely not.
BY MR. RABER:
Q. As we sit here today, do you recall whether or not you ever completed a final safety position paper after the

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June 2000 SERM?
A. I don't recall there being a final position paper.
Q. Can you explain why you don't recall one of those final documents existing?
A. It is my belief, as was then, that the FDA document, which was prepared at the same time that the initial discussion document was being written, that that FDA response document really served exactly the same purpose of a position paper in that it provided all the necessary information to the reader to see that there was insufficient evidence to suggest a causal relationship between Seroquel therapy and diabetes.
Q. And in the fall of 2000, did you have another SERM meeting coming up to consider this glucose and diabetes issue again?
A. Yes.
Q. Were you drafting documents relating to that?

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A. Yes.
Q. What were you drafting in preparation for that?
A. I was drafting an update -- a new discussion document, but it was updated from the previous one with new data.
Q. Did anybody at AstraZeneca need to have a safety position paper relating to the June SERM to take any action of any kind?
MR. PIRTLE: Objection, speculation.
THE WITNESS: No, not at all.
BY MR. RABER:
Q. If SERM is going --
If there's going to be a change in the core data sheet, what kind of document gets prepared, a justification document or a safety position paper?
A. A justification document, which sometimes now goes under the name

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of a clinical overview.
Q. All right.
Dr. Geller, I want to just talk about a few more things here. I want to have you keep Geller Exhibit 17 in front of you, and I also want to show you Geller Exhibit 30.
Now, you've testified in response to questions that you believe that Geller Exhibit 17, which is also attached to Geller Exhibit 30, is a draft of a position paper; is that right?
MR. PIRTLE: Objection to the form.
THE WITNESS: Yes. I already alluded to that, I believe, in my testimony.
BY MR. RABER:
Q. Do you recall yesterday when Mr. Pirtle leaned forward in his chair and said, I don't believe you that it's a draft. Do you remember that?
A. I do, sir.
MR. PIRTLE: Form.

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BY MR. RABER:
Q. I want to talk with you a little bit about why you believe that this safety position paper that's in front of you was not a final document. Okay?
A. Yes.
Q. All right.
Let's look at Exhibit 17, Geller Exhibit 17.
If you look at the page numbering on the bottom, do you see that?
A. Yes.
Q. What do you see when you look at the page numbering on the bottom?
A. I see in this case "Page 2 of ?."
Q. What does the presence of a question mark in the page numbering indicate to you about whether or not that is a final document?
A. It indicates that it is not a final document. It indicates that it is a draft.

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Q. In fact, the preliminary draft of your June discussion document, I think it's Defense Exhibit 202, can you tell us whether or not that draft has question marks in the page numbering?
A. Yes. This says "Page Auto," A-U-T-O, separate word "Page," P-A-G-E, "of?"
Q. Now does --
Is there any question in your mind that Defense Exhibit 202 is a draft document?
A. I'm sorry. Please repeat the question.
Q. Is there any question in your mind that that's a draft?
A. There's no question, sir.
Q. All right.
Does the word "draft" appear anywhere on Defense Exhibit 202?
A. No.
Q. Let's go back, then, to Geller Exhibit 30, which is the e-mails with your draft position paper attached.

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In your e-mail, you write to Janet Spiers attaching a "position paper and justification document for diabetes, et cetera and weight gain."
Do you see that?
A. Yes.
Q. Then you say "Vikram." Who is Vikram?
A. Vikram is Vikram Dev, who was my supervisor at the time.
Q. "Vikram has not reviewed either document as his father recently passed away and he is in India."
Do you see that?
A. I'm sorry. Can you please tell me the page number?
Q. Please look at the very first page, the e-mail from you -- at the bottom from you to Janet.
A. Here we go. I'm sorry. Yes.
Q. "Vikram has not reviewed either document as his father recently passed away and he is in India."

EXHIBIT 2

AstraZeneca Pharmaceuticals

Seroquel™
(Quetiapine)

Commercial Support Team - Technical Document (TD004)

BPRS meta-analysis

Request From:

Date Requested:

Statistician/Statistical Programmer Responsible: Rob Hemmings / Karen Melvin

1 Source of Data

Data for these analyses comes from mdata.bprs (a dataset stored in the CDE within the CST directory). This is a pooled dataset of 12 trials, each of which had either BPRS or PANSS as an endpoint. These trials represent all available data on BPRS scores from the Seroquel clinical trial program.

The creation of this dataset (handling of missing data, timing of endpoint etc.) is described in a document produced by Karen Melvin. This document is held in S:\d5077zfiles\cst\dataset creation.doc.

2 Design of Trials/ Analysis Methods

2.1 Study Design

Ten studies were selected to be used in this analysis, these are listed below:

5077IL/0004, 5077IL/0006, 204636/0007, 204636/0008, 5077IL/0013, 5077IL/0014, 5077IL/0050, 5077IL/0052, 5077IL/0053, 5077IL/0054.

The two trials omitted from the original dataset were trials 5077IL/0012 and 5077IL/0015. The former because there was no internal comparator (making model fitting difficult) and the latter because of significantly different entry criteria.

In 5 of these 10 trials, the BPRS questionnaire was used as an endpoint in the trial. In the remaining 5 trials, BPRS scores have been derived from the PANSS questionnaire which was a trial endpoint.

Comparators
The analyses performed compare Seroquel separately with each of placebo; Haloperidol; Chlorpromazine; Risperidone and 'other typicals' (defined as either Haloperidol or Chlorpromazine). Four of the trials contained comparative data against placebo; 4 against Haloperidol; 2 against Chlorpromazine; 1 against Risperidone and 6 against 'other typicals'.

Seroquel Dose

A range of doses of Seroquel were used in the above-mentioned studies, therefore each comparison was performed twice with respect to level of Seroquel dose. The first used all patients receiving therapeutic doses of Seroquel (150-750mg/day - labeled 'all doses'), the second used only patients receiving high-dose Seroquel (at least 400 mg/day - labeled 'high dose').

Categories of BPRS

The 18 point BPRS scale can either be assessed as a whole or can be sub-divided into separate item or factor scores. Assessed in these analyses were:

- Factor I (Somatic concern; Anxiety; Guilt feeling; Depressive mood) - baseline ≥ 8;
- Factor V (Hostility; Suspiciousness; Uncooperativeness) - baseline ≥ 6;
- Mood Cluster (Depressive mood; Anxiety; Guilt feelings; Tension) - baseline ≥ 8;
- Hostility Cluster (Anxiety; Tension; Hostility; Suspiciousness; Uncooperativeness; Excitement) - baseline ≥ 12;
- Hostility Item - baseline ≥ 3;
- Anxiety Item - baseline ≥ 3;
- Total BPRS score - baseline ≥ 36.

Patient Population

Though each of the above-mentioned trials may have slightly different patient populations, they were considered suitable for inclusion to this meta-analysis.
For inclusion to the analysis of each of the above categories, patients were required to be symptomatic in that category. Therefore, patients were not included in the analysis of a particular category unless their baseline score was at least that denoted above (note baselines are denoted as totals within each category). In addition, patients were excluded if their disease type did not match that recognised for Seroquel use in Europe.

2.2 Analysis Methods

Two endpoints were assessed in this meta-analysis.

Firstly, a 'change from baseline' score. This was calculated separately for each category and analysed via analysis of covariance (ANCOVA) using PROC MIXED in SAS, with the baseline appropriate to that category included in the model as a covariate. A term was also included in the model for 'trial'. Also assessed were trial*treatment and covariate*treatment interactions, though these were subsequently dropped from the model unless a consistent pattern of significance of these terms could be identified across each of the endpoints assessed. The standard checks of normality assumptions behind ANCOVA were performed.

Secondly the 'proportion of responders' was analysed. A responder was defined as any patient with at least a 40% drop in score from baseline to endpoint. These data were analysed using PROC GENMOD in SAS. The model used was similar to that described for the change from baseline endpoint above.

For each endpoint, both an 'observed cases' (OC) and a 'last value carried forward' (LVCF) analysis was performed.

In total, this BPRS meta-analysis has involved 7 categories of the BPRS scale, each to be assessed against 5 comparators, using 2 endpoints, each derived in two different ways (OC and LVCF). Each analysis was then performed for 2 cuts of the SEROQUEL data (by mean dose received). This makes a total of 280 separate p-values being generated. By chance alone we expect 1 in 20 p-values to be significant, therefore isolated significant p-values will be ignored, instead interpretation of the analyses will look for patterns of significant results, either across particular categories of the BPRS or against particular comparators.

2.3 Details of SAS programs

All analysis programs are stored in the CDE under the CST directory (s:\d5077\filesm\CST).

The programs used to create the mdata.bprs dataset are described in Karen's document. The programs performing the statistical analyses are:

- TD4_X1 - change from baseline analysis;
- TD4_X1A - change from baseline analysis (high doses of SEROQUEL);
- TD4_X1B - change from baseline analysis ('other typicals');
- TD4_X1C - change from baseline analysis (high dose of SEROQUEL versus 'other typicals);
- TD4_X2 - proportion of responders;
- TD4_X2A - proportion of responders (high doses of SEROQUEL);
- TD4_X2B - proportion of responders ('other typicals');
- TD4_X2C - proportion of responders (high dose of SEROQUEL versus 'other typicals).

In addition to this, baseline scores were investigated to ensure that BPRS scores derived respectively from BPRS and PANSS questionnaires could be combined. The programs producing these baseline plots are: TD4_BASE; TD4_2BAS.

3 Results

As described above, a very large number of analyses have been performed on these data, so the results of the analyses will necessarily be described in general terms. Initially, significant results will be discussed. Any trends observed in the data will then be highlighted.

<u>Change from baseline</u>

In each of the 7 categories, Seroquel proved to be significantly better than placebo (regardless of whether 'all doses' or only high-doses of Seroquel were used). In each case this improvement was observed using an LVCF approach, however for total

BPRS score using all Seroquel data, this result was supported by the observed cases analysis.
The pattern was less obvious when Seroquel was compared with Haloperidol. Against 'all doses' of Seroquel, each of the 3 significant p-values generated was in favour of Haloperidol (Total BPRS, Factor V and Hostility Cluster). There was no evidence of significant differences between the treatments when Haloperidol was compared to high-dose Seroquel.
No statistically significant differences were observed for any of the categories when Seroquel was compared with Chlorpromazine.
Comparisons against Risperidone used only trial 5077IL/0053. Against 'all doses' of Seroquel, Risperidone showed significant improvement on Factor V scores and the Hostility Cluster. Against high-dose Seroquel only, these two categories were again significantly in favour of Risperidone, along with the Anxiety Item, Total BPRS and the Mood cluster.
Against either Chlorpromazine or Haloperidol, LVCF analyses showed a significant improvement against Seroquel for Total BPRS, Factor V and the Hostility Cluster, though these differences were removed when assessing high-dose of Seroquel only.

For 'all doses' of Seroquel, trends were observed for the Factor I cluster in which a positive, though non-significant estimate of treatment effect was observed. This was also true for the Mood cluster (with the exception of comparisons versus Risperidone). For high doses of Seroquel, the Factor I cluster again showed mainly positive treatment effects (excepting Risperidone), however no trends were apparent in any of the other categories.

A full set of results, showing least square mean changes from baseline for each treatment group, an estimate of treatment effect (difference in lsmeans) with 95% confidence interval and associated p-value are presented in Appendix A.

Proportion of responders

Seroquel ('all doses') proved to be significantly better than placebo for 4 of the 7 categories as assessed by this endpoint (total BPRS, Factor V, Hostility Cluster, Mood Cluster) and tended toward significance in the Anxiety and Hostility items. A very similar pattern was observed for high doses of Seroquel only against placebo. In each of the 4 cases the improvement was observed using an LVCF approach.
The pattern was less obvious when Seroquel was compared with Haloperidol. Against 'all doses' of Seroquel, only Factor V showed a significant difference between the treatments - in favour of Haloperidol. As for the change from baseline analysis, this difference disappeared when comparing against only high-doses of Seroquel.
Again, no statistically significant results were obtained when Seroquel was compared with Chlorpromazine.
Comparisons against Risperidone using all doses of Seroquel showed significant improvement for Risperidone on total BPRS, Factor V scores and the Hostility Cluster. Against high-dose Seroquel only, the Anxiety item, Factor I and Mood cluster scores were also significantly in favour of Risperidone.
Against either Chlorpromazine or Haloperidol, LVCF analyses showed a significant improvement against 'all doses' of Seroquel for Factor V, though this difference were removed when assessing high-dose of Seroquel only.

As above, the more positive trends for Seroquel were observed on the Factor I and Mood cluster items, though no significant differences were found in favour of Seroquel other than against placebo.

A full set of results, showing percentage of responders for each treatment group, odds ratios and 95% confidence intervals with associated p-value are presented in Appendix A.

The following table is an attempt to simplify the claims that could be obtained from these results. A ✓ is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or using LVCF. A ✗ marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

Table 1

Comparator	Category						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✗	-	✗	-	✗	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✗	✗	✗	✗	-	✗	✗
Other typicals	-	✗	-	✗	-	✗	-

4 Conclusions

In terms of generating positive claims for Seroquel, these analyses seem somewhat disappointing. Although some trends in favour of Seroquel were observed in the Factor I and Mood cluster items, there was no evidence in these analyses of a significant benefit for using Seroquel over any other of the active agents assessed. There was, however, consistent evidence that Seroquel is better than placebo for a number of the BPRS sub-categories assessed.

There was little evidence of improvement with high-doses of Seroquel relative to including 'all doses' of Seroquel, though in the Haloperidol studies some of the statistically significant disadvantages were removed when looking at high doses only. In contrast, in the comparisons against Risperidone (trial 5077IL/0053), looking at high doses of Seroquel appears to give relatively worse results than looking at all patients together.

In general, the analysis of the two endpoints of mean change from baseline and proportion of responders gave similar conclusions.

5 References

No references were used.

Appendix A: Statistical Appendix

Index of Tables Created

TITLE

Key: VAR - Category of BPRS being assessed (Anxiety Item, Total BPRS; Factor I; Factor V; Hostility Item; Hostility Cluster; Mood Cluster).
COMP - Comparator
LSCOMP - least square mean of comparator
LSSER - least square mean of Seroquel
EST - Estimate of treatment effect (either difference in lsmeans or odds ratio)
P_T - p-value
LOWER / LCL - 95% lower confidence interval bound
UPPER / UCL - 95% upper confidence interval bound
ANAL - OBSERVED CASES or LVCF analysis
SIG - * denotes statistical significance
SERN - Number of patients on Seroquel
SERR - Number of responders on Seroquel
SER% - Percentage of responders on Seroquel
COMPN - Number of patients on comparator
COMPR - Number of responders on comparator
COMP% - Percentage of responders on comparator

TABLE T1 Change from baseline analyses - all doses of Seroquel

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	ANAL	SIG
1	-1.92888240	ENDANX	PLA	-2.16321932	0.23433692	0.2397	-0.1574	0.6261	OBSERVED CASES	
2	-1.22148681	ENDANX	PLA	-1.65696543	0.43547863	0.0070	0.1198	0.7512	LVCF	*
3	-1.64311081	ENDANX	HAL	-1.81583045	0.17271963	0.2842	-0.1441	0.4895	OBSERVED CASES	
4	-1.09703883	ENDANX	HAL	-1.23353560	0.13649677	0.3027	-0.1234	0.3964	LVCF	
5	-1.87706692	ENDANX	CHL	-1.80553924	-0.07152768	0.7017	-0.4395	0.2964	OBSERVED CASES	
6	-1.52013169	ENDANX	CHL	-1.47974816	-0.04038353	0.8284	-0.4070	0.3263	LVCF	
7	-1.96801427	ENDANX	RIS	-2.00028493	0.03227066	0.8844	-0.4066	0.4712	OBSERVED CASES	
8	-1.46212777	ENDANX	RIS	-1.38227098	-0.07985680	0.7155	-0.5116	0.3518	LVCF	
9	-17.76054585	ENDBPRS	PLA	-24.83229285	7.07174700	0.0039	2.2999	11.8436	OBSERVED CASES	*
10	-3.29219461	ENDBPRS	PLA	-12.10226823	8.81007362	0.0001	5.4671	12.1531	LVCF	*
11	-20.50075645	ENDBPRS	HAL	-19.87384433	-0.62691212	0.6831	-3.6447	2.3909	OBSERVED CASES	
12	-13.24621220	ENDBPRS	HAL	-9.93053659	-3.31567561	0.0145	-5.9713	-0.6600	LVCF	*
13	-22.13053657	ENDBPRS	CHL	-21.67375945	-0.45677712	0.8012	-4.0275	3.1139	OBSERVED CASES	
14	-17.75196333	ENDBPRS	CHL	-17.26124270	-0.49072063	0.7930	-4.1681	3.1867	LVCF	
15	-23.87001671	ENDBPRS	RIS	-24.11188221	0.24186550	0.9019	-3.6315	4.1152	OBSERVED CASES	
16	-19.45877126	ENDBPRS	RIS	-16.29780780	-3.16096346	0.1581	-7.5608	1.2388	LVCF	
17	-5.97958774	ENDFI	PLA	-6.95215090	0.97256316	0.1030	-0.1984	2.1435	OBSERVED CASES	
18	-3.75138902	ENDFI	PLA	-5.26858020	1.51719118	0.0024	0.5412	2.4932	LVCF	*
19	-5.01792808	ENDFI	HAL	-5.52521580	0.50728772	0.2369	-0.3349	1.3495	OBSERVED CASES	
20	-3.20544661	ENDFI	HAL	-3.47503972	0.26959311	0.4574	-0.4425	0.9817	LVCF	
21	-5.59177074	ENDFI	CHL	-6.35956050	0.76778976	0.1385	-0.2509	1.7865	OBSERVED CASES	
22	-4.60027853	ENDFI	CHL	-5.12941442	0.52913590	0.3319	-0.5437	1.6019	LVCF	
23	-5.15051726	ENDFI	RIS	-5.96312710	0.81260984	0.2096	-0.4636	2.0888	OBSERVED CASES	
24	-4.25134959	ENDFI	RIS	-4.29459640	0.04324681	0.9417	-1.1229	1.2093	LVCF	
25	-3.39572940	ENDFV	PLA	-4.46652537	1.07079596	0.0867	-0.1559	2.2974	OBSERVED CASES	
26	-1.35968707	ENDFV	PLA	-3.06318005	1.70349297	0.0003	0.7818	2.6252	LVCF	*
27	-4.32580592	ENDFV	HAL	-4.09406696	-0.23173895	0.4981	-0.9038	0.4403	OBSERVED CASES	
28	-3.04323303	ENDFV	HAL	-1.67985602	-1.36337701	0.0001	-2.0111	-0.7157	LVCF	*
29	-4.94827119	ENDFV	CHL	-4.54810579	-0.40016540	0.3761	-1.2899	0.4896	OBSERVED CASES	
30	-3.68675735	ENDFV	CHL	-3.42537388	-0.26138347	0.5942	-1.2262	0.7034	LVCF	
31	-5.54643474	ENDFV	RIS	-4.64890205	-0.89753268	0.0453	-1.7758	-0.0192	OBSERVED CASES	*
32	-4.12803635	ENDFV	RIS	-2.76431072	-1.36372563	0.0113	-2.4150	-0.3124	LVCF	*
33	-1.24805589	ENDHOST	PLA	-1.63088616	0.38283027	0.2615	-0.2898	1.0555	OBSERVED CASES	
34	-0.46937795	ENDHOST	PLA	-1.05716657	0.58778862	0.0155	0.1129	1.0627	LVCF	*
35	-2.09204701	ENDHOST	HAL	-2.17564885	0.08360184	0.7463	-0.4267	0.5939	OBSERVED CASES	
36	-1.56003798	ENDHOST	HAL	-1.17563778	-0.38440019	0.1020	-0.8457	0.0769	LVCF	
37	-2.14402246	ENDHOST	CHL	-2.13340168	-0.01062078	0.9632	-0.4658	0.4445	OBSERVED CASES	
38	-1.70533282	ENDHOST	CHL	-1.58320219	-0.12213063	0.6438	-0.6430	0.3987	LVCF	

39	-2.38373083	ENDHOST	RIS	-2.27768313	-0.10604770	0.7365	-0.7367	0.5246	OBSERVED CASES	
40	-2.02228254	ENDHOST	RIS	-1.40345663	-0.61882591	0.1169	-1.3966	0.1590	LVCF	
41	-7.58622096	ENDJMCK	PLA	-9.20592510	1.61970414	0.1167	-0.4079	3.6473	OBSERVED CASES	
42	-1.58099388	ENDJMCK	PLA	-4.56653108	2.98553719	0.0002	1.4067	4.5644	LVCF	*
43	-7.81202611	ENDJMCK	HAL	-7.60864672	-0.20337939	0.7424	-1.4194	1.0127	OBSERVED CASES	
44	-4.81841620	ENDJMCK	HAL	-3.50475023	-1.31366597	0.0267	-2.4748	-0.1526	LVCF	*
45	-9.48084330	ENDJMCK	CHL	-8.21072808	-1.27011522	0.1128	-2.8427	0.3024	OBSERVED CASES	
46	-7.06886652	ENDJMCK	CHL	-5.94149790	-1.12736863	0.2196	-2.9311	0.6764	LVCF	
47	-10.06303733	ENDJMCK	RIS	-8.79758485	-1.26545248	0.1184	-2.8576	0.3267	OBSERVED CASES	
48	-7.72743912	ENDJMCK	RIS	-4.78555086	-2.94188826	0.0022	-4.8135	-1.0702	LVCF	*
49	-6.06556776	ENDMOOD	PLA	-6.74951208	0.68394433	0.2579	-0.5051	1.8730	OBSERVED CASES	
50	-3.12900293	ENDMOOD	PLA	-4.94488213	1.81587920	0.0001	0.8876	2.7442	LVCF	*
51	-5.02980482	ENDMOOD	HAL	-5.45043252	0.42062770	0.3317	-0.4306	1.2719	OBSERVED CASES	
52	-3.19803087	ENDMOOD	HAL	-3.29500962	0.09697875	0.7915	-0.6231	0.8171	LVCF	
53	-6.02250350	ENDMOOD	CHL	-6.43589786	0.41339435	0.4230	-0.6031	1.4298	OBSERVED CASES	
54	-4.94702421	ENDMOOD	CHL	-5.01676714	0.06974293	0.9007	-1.0306	1.1701	LVCF	
55	-5.80608660	ENDMOOD	RIS	-6.24701590	0.44092930	0.4473	-0.7039	1.5857	OBSERVED CASES	
56	-4.58206556	ENDMOOD	RIS	-4.48510122	-0.09696434	0.8646	-1.2167	1.0227	LVCF	

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	SIG	ANAL
1	-1.79389637	ENDANX	CHLOR + HAL	-1.86827025	0.07437388	0.5665	-0.1805	0.3292		OBSERVED CASES
2	-1.34183576	ENDANX	CHLOR + HAL	-1.36361603	0.02178027	0.8554	-0.2129	0.2565		LVCF
3	-21.58305415	ENDBPRS	CHLOR + HAL	-21.36233494	-0.22071921	0.8578	-2.6396	2.1981		OBSERVED CASES
4	-15.56831038	ENDBPRS	CHLOR + HAL	-12.94068905	-2.62762133	0.0302	-5.0029	-0.2524	*	LVCF
5	-5.29156414	ENDFI	CHLOR + HAL	-5.85050268	0.55893853	0.1077	-0.1227	1.2406		OBSERVED CASES
6	-3.83463775	ENDFI	CHLOR + HAL	-4.02731873	0.19268098	0.5522	-0.4435	0.8288		LVCF
7	-4.73066465	ENDFV	CHLOR + HAL	-4.46158711	-0.26907754	0.3340	-0.8158	0.2777		OBSERVED CASES
8	-3.47305920	ENDFV	CHLOR + HAL	-2.41828126	-1.05477795	0.0004	-1.6334	-0.4762	*	LVCF
9	-2.22606169	ENDHOST	CHLOR + HAL	-2.36440571	0.13834401	0.4211	-0.2001	0.4768		OBSERVED CASES
10	-1.66087953	ENDHOST	CHLOR + HAL	-1.46361825	-0.19726128	0.3046	-0.5747	0.1802		LVCF
11	-8.71122711	ENDJMCK	CHLOR + HAL	-8.08021617	-0.63101094	0.2213	-1.6435	0.3815		OBSERVED CASES
12	-6.01005250	ENDJMCK	CHLOR + HAL	-4.55178363	-1.45826887	0.0078	-2.5312	-0.3853	*	LVCF
13	-5.54239435	ENDMOOD	CHLOR + HAL	-5.92187829	0.37948394	0.2860	-0.3188	1.0777		OBSERVED CASES
14	-3.98221893	ENDMOOD	CHLOR + HAL	-3.96771977	-0.01449915	0.9658	-0.6784	0.6494		LVCF

TABLE T2 Change from baseline analyses - high doses of Seroquel only

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	ANAL	SIG
1	-1.86002641	ENDANX	PLA	-1.89606302	0.03603661	0.8789	-0.4310	0.5030	OBSERVED CASES	
2	-1.11975252	ENDANX	PLA	-1.78884859	0.66909607	0.0006	0.2921	1.0461	LVCF	*
3	-1.59109117	ENDANX	HAL	-1.64386973	0.05277856	0.7670	-0.2978	0.4033	OBSERVED CASES	
4	-1.06312514	ENDANX	HAL	-1.30147985	0.23835471	0.1093	-0.0536	0.5304	LVCF	
5	-1.89249276	ENDANX	CHL	-1.78497344	-0.10751932	0.5883	-0.4990	0.2840	OBSERVED CASES	
6	-1.54665474	ENDANX	CHL	-1.48872100	-0.05793374	0.7723	-0.4522	0.3363	LVCF	
7	-2.01077886	ENDANX	RIS	-1.34670550	-0.66407335	0.0196	-1.2188	-0.1093	OBSERVED CASES	*
8	-1.49368861	ENDANX	RIS	-1.06956530	-0.42412331	0.1523	-1.0071	0.1588	LVCF	
9	-12.37181763	ENDBPRS	PLA	-17.70516480	5.33334716	0.0633	-0.2998	10.9665	OBSERVED CASES	
10	1.92442320	ENDBPRS	PLA	-9.05845346	10.98287666	0.0001	6.9911	14.9746	LVCF	*
11	-20.60733481	ENDBPRS	HAL	-17.94615278	-2.66118203	0.1137	-5.9627	0.6404	OBSERVED CASES	
12	-13.07277770	ENDBPRS	HAL	-10.93796166	-2.13481604	0.1576	-5.0989	0.8292	LVCF	
13	-22.18010978	ENDBPRS	CHL	-21.09511723	-1.08499254	0.5766	-4.9115	2.7415	OBSERVED CASES	
14	-17.78622375	ENDBPRS	CHL	-17.94716357	0.16093982	0.9357	-3.7650	4.0869	LVCF	
15	-23.87226225	ENDBPRS	RIS	-16.11690026	-7.75536199	0.0010	-12.3094	-3.2013	OBSERVED CASES	*
16	-19.43587302	ENDBPRS	RIS	-14.03920633	-5.39666670	0.0483	-10.7530	-0.0403	LVCF	*
17	-5.33815164	ENDFI	PLA	-5.66256394	0.32441230	0.6460	-1.0717	1.7206	OBSERVED CASES	
18	-2.92912778	ENDFI	PLA	-4.78898154	1.85985376	0.0025	0.6620	3.0577	LVCF	*
19	-4.91747782	ENDFI	HAL	-5.01335594	0.09587812	0.8379	-0.8264	1.0181	OBSERVED CASES	
20	-3.14125964	ENDFI	HAL	-3.71357248	0.57231284	0.1683	-0.2429	1.3875	LVCF	
21	-5.61517512	ENDFI	CHL	-6.26132346	0.64614835	0.2370	-0.4298	1.7221	OBSERVED CASES	
22	-4.63766965	ENDFI	CHL	-5.20598269	0.56831304	0.3264	-0.5713	1.7079	LVCF	
23	-5.15138965	ENDFI	RIS	-4.17475898	-0.97663067	0.1900	-2.4464	0.4932	OBSERVED CASES	
24	-4.24152962	ENDFI	RIS	-4.07587467	-0.16565495	0.8215	-1.6166	1.2853	LVCF	
25	-2.47225948	ENDFV	PLA	-3.36632258	0.89406310	0.2675	-0.6957	2.4839	OBSERVED CASES	
26	0.05125015	ENDFV	PLA	-2.58746679	2.63871693	0.0001	1.4935	3.7839	LVCF	*
27	-4.36108417	ENDFV	HAL	-4.02115444	-0.33992973	0.3603	-1.0702	0.3904	OBSERVED CASES	
28	-2.99474409	ENDFV	HAL	-2.34345872	-0.65128537	0.0677	-1.3502	0.0476	LVCF	
29	-4.94358920	ENDFV	CHL	-4.31140900	-0.63218020	0.1962	-1.5938	0.3295	OBSERVED CASES	
30	-3.68852378	ENDFV	CHL	-3.38474114	-0.30378264	0.5655	-1.3438	0.7362	LVCF	
31	-5.57247882	ENDFV	RIS	-3.17936878	-2.39311003	0.0001	-3.4499	-1.3363	OBSERVED CASES	*
32	-4.15897803	ENDFV	RIS	-2.70767998	-1.45129805	0.0368	-2.8124	-0.0902	LVCF	*
33	-1.23889365	ENDHOST	PLA	-1.72895804	0.49006439	0.2205	-0.3017	1.2818	OBSERVED CASES	
34	-0.41106989	ENDHOST	PLA	-1.49663968	1.08556979	0.0002	0.5253	1.6459	LVCF	*
35	-2.11643366	ENDHOST	HAL	-2.13421944	0.01778577	0.9476	-0.5177	0.5533	OBSERVED CASES	

36	-1.57249014	ENDHOST	HAL	-1.52913520	-0.04335494	0.8571	-0.5178	0.4311	LVCF	
37	-2.15169346	ENDHOST	CHL	-2.08561463	-0.06607884	0.7969	-0.5743	0.4421	OBSERVED CASES	
38	-1.72271481	ENDHOST	CHL	-1.60957163	-0.11314318	0.6975	-0.6876	0.4613	LVCF	
39	-2.43329859	ENDHOST	RIS	-2.02240750	-0.41089109	0.3877	-1.3646	0.5428	OBSERVED CASES	
40	-2.02411142	ENDHOST	RIS	-1.85877596	-0.16533546	0.7800	-1.3501	1.0195	LVCF	
41	-5.60851358	ENDJMCK	PLA	-6.79468075	1.18616717	0.3366	-1.2490	3.6213	OBSERVED CASES	
42	0.15085958	ENDJMCK	PLA	-4.47356794	4.62442752	0.0001	2.7161	6.5328	LVCF	*
43	-7.94031667	ENDJMCK	HAL	-7.29773930	-0.64257737	0.3438	-1.9765	0.6913	OBSERVED CASES	
44	-4.74070420	ENDJMCK	HAL	-4.25545285	-0.48525135	0.4541	-1.7582	0.7877	LVCF	
45	-9.48625190	ENDJMCK	CHL	-7.97775099	-1.50850091	0.0808	-3.2040	0.1870	OBSERVED CASES	
46	-7.06362286	ENDJMCK	CHL	-5.97633527	-1.08728759	0.2691	-3.0210	0.8464	LVCF	
47	-10.12324070	ENDJMCK	RIS	-5.60285644	-4.52038426	0.0001	-6.4103	-2.6305	OBSERVED CASES	*
48	-7.80928475	ENDJMCK	RIS	-4.13101782	-3.67826693	0.0030	-6.0835	-1.2730	LVCF	*
49	-5.62749649	ENDMOOD	PLA	-5.45764233	-0.16985416	0.8098	-1.5648	1.2251	OBSERVED CASES	
50	-2.61444904	ENDMOOD	PLA	-4.82320777	2.20875873	0.0001	1.0947	3.3228	LVCF	*
51	-4.90700396	ENDMOOD	HAL	-4.77209872	-0.13490524	0.7806	-1.0875	0.8177	OBSERVED CASES	
52	-3.11911109	ENDMOOD	HAL	-3.62295343	0.50384234	0.2252	-0.3116	1.3193	LVCF	
53	-6.01787574	ENDMOOD	CHL	-6.34122818	0.32335243	0.5532	-0.7520	1.3987	OBSERVED CASES	
54	-4.96993289	ENDMOOD	CHL	-4.97172332	0.00179043	0.9976	-1.1695	1.1731	LVCF	
55	-5.79496411	ENDMOOD	RIS	-4.04830400	-1.74666011	0.0156	-3.1544	-0.3389	OBSERVED CASES	*
56	-4.55460111	ENDMOOD	RIS	-3.71002082	-0.84458028	0.2451	-2.2755	0.5863	LVCF	

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	SIG	ANAL
1	-1.76707457	ENDANX	CHLOR + HAL	-1.75815550	-0.00891907	0.9494	-0.2852	0.2674		OBSERVED CASES
2	-1.34475999	ENDANX	CHLOR + HAL	-1.42217172	0.07741173	0.5584	-0.1823	0.3371		LVCF
3	-21.71790120	ENDBPRS	CHLOR + HAL	-20.06123241	-1.65666879	0.2168	-4.2892	0.9759		OBSERVED CASES
4	-15.71720341	ENDBPRS	CHLOR + HAL	-14.29704250	-1.42016091	0.2815	-4.0079	1.1676		LVCF
5	-5.28710769	ENDFI	CHLOR + HAL	-5.56411911	0.27701141	0.4618	-0.4626	1.0166		OBSERVED CASES
6	-3.85988690	ENDFI	CHLOR + HAL	-4.27867823	0.41879133	0.2505	-0.2964	1.1339		LVCF
7	-4.75713631	ENDFV	CHLOR + HAL	-4.33339252	-0.42374379	0.1629	-1.0197	0.1722		OBSERVED CASES
8	-3.51044253	ENDFV	CHLOR + HAL	-2.93657933	-0.57386319	0.0716	-1.1984	0.0507		LVCF
9	-2.23114003	ENDHOST	CHLOR + HAL	-2.31125371	0.08011368	0.6671	-0.2869	0.4471		OBSERVED CASES
10	-1.71941743	ENDHOST	CHLOR + HAL	-1.72362724	0.00420981	0.9832	-0.3886	0.3970		LVCF
11	-8.80937945	ENDJMCK	CHLOR + HAL	-7.77454339	-1.03483606	0.0645	-2.1320	0.0624		OBSERVED CASES
12	-6.03853602	ENDJMCK	CHLOR + HAL	-5.13024481	-0.90829122	0.1255	-2.0711	0.2545		LVCF
13	-5.54214234	ENDMOOD	CHLOR + HAL	-5.61075894	0.06861661	0.8604	-0.6982	0.8355		OBSERVED CASES
14	-4.00945108	ENDMOOD	CHLOR + HAL	-4.31670134	0.30725027	0.4142	-0.4314	1.0459		LVCF

TABLE T3 Proportion of responders - all doses of Seroquel

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	0.74012	0.36442	1.50316	0.40512	160	68	42.5000	56	24	42.8571	
2	PLA	RESPANX	LVCF	0.62955	0.38382	1.03262	0.06682	307	99	32.2476	123	35	28.4553	
3	PLA	RESPBPRS	OBSERVED CASES	0.46342	0.21431	1.00210	0.05062	148	72	48.6486	41	15	36.5854	
4	PLA	RESPBPRS	LVCF	0.34725	0.19061	0.63258	0.00055	304	87	28.6184	115	17	14.7826	*
5	PLA	RESPFI	OBSERVED CASES	0.65689	0.31573	1.36670	0.26091	141	82	58.1560	49	28	57.1429	
6	PLA	RESPFI	LVCF	0.67151	0.41248	1.09322	0.10926	261	114	43.6782	108	43	39.8148	
7	PLA	RESPFV	OBSERVED CASES	0.56606	0.28394	1.12848	0.10596	144	82	56.9444	48	22	45.8333	
8	PLA	RESPFV	LVCF	0.46766	0.28284	0.77324	0.00305	288	106	36.8056	120	30	25.0000	*
9	PLA	RESPHOST	OBSERVED CASES	2.31667	0.86413	6.21083	0.09497	79	35	44.3038	26	17	65.3846	
10	PLA	RESPHOST	LVCF	0.73154	0.39894	1.34143	0.31225	171	73	42.6901	66	26	39.3939	
11	PLA	RESPJMCK	OBSERVED CASES	0.67637	0.32345	1.41436	0.29885	141	81	57.4468	46	25	54.3478	
12	PLA	RESPJMCK	LVCF	0.53356	0.32427	0.87796	0.01343	297	103	34.6801	121	32	26.4463	*
13	PLA	RESPMOOD	OBSERVED CASES	0.60295	0.27408	1.32642	0.20849	151	88	58.2781	45	27	60.0000	
14	PLA	RESPMOOD	LVCF	0.47078	0.28393	0.78059	0.00350	284	119	41.9014	116	38	32.7586	*
15	HAL	RESPANX	OBSERVED CASES	1.10065	0.66436	1.82346	0.70965	188	96	51.0638	131	78	59.5420	
16	HAL	RESPANX	LVCF	1.00224	0.69463	1.44607	0.99046	350	128	36.5714	229	99	43.2314	
17	HAL	RESPBPRS	OBSERVED CASES	0.82711	0.52225	1.30993	0.41843	209	117	55.9809	164	96	58.5366	
18	HAL	RESPBPRS	LVCF	1.04784	0.74126	1.48120	0.79132	381	129	33.8583	262	107	40.8397	
19	HAL	RESPFI	OBSERVED CASES	0.80527	0.50046	1.29573	0.37215	185	108	58.3784	151	83	54.9669	
20	HAL	RESPFI	LVCF	0.88699	0.62842	1.25195	0.49521	352	145	41.1932	260	106	40.7692	
21	HAL	RESPFV	OBSERVED CASES	1.14320	0.70212	1.86136	0.59052	190	117	61.5789	168	118	70.2381	
22	HAL	RESPFV	LVCF	1.53737	1.08756	2.17323	0.01488	359	138	38.4401	262	145	55.3435	*
23	HAL	RESPHOST	OBSERVED CASES	0.80849	0.32541	2.00871	0.64707	71	42	59.1549	61	43	70.4918	
24	HAL	RESPHOST	LVCF	1.16633	0.63650	2.13721	0.61853	153	72	47.0588	94	59	62.7660	
25	HAL	RESPJMCK	OBSERVED CASES	0.90595	0.56277	1.45843	0.68432	197	117	59.3909	163	102	62.5767	
26	HAL	RESPJMCK	LVCF	1.02574	0.72369	1.45384	0.88646	366	136	37.1585	264	117	44.3182	
27	HAL	RESPMOOD	OBSERVED CASES	0.83245	0.52485	1.32032	0.43584	196	111	56.6327	151	82	54.3046	
28	HAL	RESPMOOD	LVCF	0.91593	0.65226	1.28618	0.61217	367	144	39.2371	262	104	39.6947	
29	CHL	RESPANX	OBSERVED CASES	0.87515	0.47998	1.59568	0.66344	98	58	59.1837	86	49	56.9767	
30	CHL	RESPANX	LVCF	1.00451	0.60414	1.67019	0.98617	124	61	49.1935	120	60	50.0000	
31	CHL	RESPBPRS	OBSERVED CASES	1.00690	0.56956	1.78005	0.98113	111	64	57.6577	109	62	56.8807	
32	CHL	RESPBPRS	LVCF	0.97390	0.60221	1.57500	0.91413	141	68	48.2270	148	70	47.2973	
33	CHL	RESPFI	OBSERVED CASES	0.78230	0.38669	1.58265	0.49465	81	59	72.8395	70	47	67.1429	
34	CHL	RESPFI	LVCF	0.87010	0.49762	1.52139	0.62549	105	61	58.0952	98	53	54.0816	
35	CHL	RESPFV	OBSERVED CASES	1.62199	0.86998	3.02405	0.12807	99	61	61.6162	100	72	72.0000	
36	CHL	RESPFV	LVCF	1.39066	0.84854	2.27915	0.19075	128	64	50.0000	142	83	58.4507	
37	CHL	RESPHOST	OBSERVED CASES	0.94059	0.38535	2.29587	0.89299	57	44	77.1930	56	42	75.0000	
38	CHL	RESPHOST	LVCF	0.95070	0.48734	1.85460	0.88211	72	48	66.6667	85	55	64.7059	

39	CHL	RESPJMCK	OBSERVED CASES	1.54632	0.83661	2.85809	0.16429	106	66	62.2642	99	70	70.7071	
40	CHL	RESPJMCK	LVCF	1.32930	0.81525	2.16749	0.25381	132	67	50.7576	141	81	57.4468	
41	CHL	RESPMOOD	OBSERVED CASES	0.86218	0.43889	1.69372	0.66687	86	61	70.9302	81	55	67.9012	
42	CHL	RESPMOOD	LVCF	1.16473	0.67777	2.00154	0.58095	111	62	55.8559	112	66	58.9286	
43	RIS	RESPANX	OBSERVED CASES	1.05654	0.48008	2.32521	0.89129	56	38	67.8571	64	45	70.3125	
44	RIS	RESPANX	LVCF	1.04980	0.58503	1.88381	0.87059	92	47	51.0870	94	50	53.1915	
45	RIS	RESPBPRS	OBSERVED CASES	2.03711	0.98478	4.21394	0.05503	67	44	65.6716	87	69	79.3103	
46	RIS	RESPBPRS	LVCF	2.26644	1.29137	3.97777	0.00436	98	47	47.9592	111	75	67.5676	*
47	RIS	RESPFI	OBSERVED CASES	1.12183	0.50245	2.50477	0.77907	55	38	69.0909	60	43	71.6667	
48	RIS	RESPFI	LVCF	1.47727	0.81762	2.66911	0.19606	91	47	51.6484	90	55	61.1111	
49	RIS	RESPFV	OBSERVED CASES	2.77949	1.17282	6.58719	0.02023	64	46	71.8750	82	72	87.8049	*
50	RIS	RESPFV	LVCF	2.26563	1.27812	4.01611	0.00511	95	49	51.5789	113	80	70.7965	*
51	RIS	RESPHOST	OBSERVED CASES	0.81567	0.17382	3.82769	0.79617	18	15	83.3333	32	26	81.2500	
52	RIS	RESPHOST	LVCF	1.22882	0.40973	3.68531	0.71308	26	18	69.2308	41	30	73.1707	
53	RIS	RESPJMCK	OBSERVED CASES	2.64135	1.19359	5.84517	0.01655	73	51	69.8630	85	73	85.8824	*
54	RIS	RESPJMCK	LVCF	2.76130	1.59364	4.78449	0.00029	115	54	46.9565	113	80	70.7965	*
55	RIS	RESPMOOD	OBSERVED CASES	0.95115	0.43766	2.06714	0.89938	64	47	73.4375	72	53	73.6111	
56	RIS	RESPMOOD	LVCF	1.17261	0.66606	2.06441	0.58109	97	53	54.6392	104	62	59.6154	

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	CHL + HAL	RESPANX	OBSERVED CASES	1.00005	0.68005	1.47063	0.99978	286	154	53.8462	217	127	58.5253	
2	CHL + HAL	RESPANX	LVCF	1.00444	0.74656	1.35139	0.97665	474	189	39.8734	349	159	45.5587	
3	CHL + HAL	RESPBPRS	OBSERVED CASES	0.89641	0.62734	1.28090	0.54817	320	181	56.5625	273	158	57.8755	
4	CHL + HAL	RESPBPRS	LVCF	1.02459	0.77376	1.35674	0.86535	522	197	37.7395	410	177	43.1707	
5	CHL + HAL	RESPFI	OBSERVED CASES	0.80208	0.54104	1.18907	0.27224	266	167	62.7820	221	130	58.8235	
6	CHL + HAL	RESPFI	LVCF	0.87916	0.65594	1.17834	0.38879	457	206	45.0766	358	159	44.4134	
7	CHL + HAL	RESPFV	OBSERVED CASES	1.32579	0.90544	1.94128	0.14721	289	178	61.5917	268	190	70.8955	
8	CHL + HAL	RESPFV	LVCF	1.48572	1.11989	1.97105	0.00605	487	202	41.4784	404	228	56.4356	*
9	CHL + HAL	RESPHOST	OBSERVED CASES	0.87307	0.46250	1.64812	0.67541	128	86	67.1875	117	85	72.6496	
10	CHL + HAL	RESPHOST	LVCF	1.06334	0.67852	1.66642	0.78875	225	120	53.3333	179	114	63.6872	
11	CHL + HAL	RESPJMCK	OBSERVED CASES	1.11128	0.76458	1.61519	0.58023	303	183	60.3960	262	172	65.6489	
12	CHL + HAL	RESPJMCK	LVCF	1.11776	0.84221	1.48346	0.44078	498	203	40.7631	405	198	48.8889	
13	CHL + HAL	RESPMOOD	OBSERVED CASES	0.84641	0.57930	1.23667	0.38870	282	172	60.9929	232	137	59.0517	
14	CHL + HAL	RESPMOOD	LVCF	0.97218	0.73004	1.29462	0.84689	478	206	43.0962	374	170	45.4545	

TABLE T4 Proportion of responders - high doses of Seroquel

OBS	COMP	END	ANAL		EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	1.00609	0.42910	2.3589	0.98887	78	29	37.1795	56	24	42.8571		
2	PLA	RESPANX	LVCF	0.55862	0.29316	1.0645	0.07671	115	35	30.4348	123	35	28.4553		
3	PLA	RESPBPRS	OBSERVED CASES	0.57553	0.24076	1.3758	0.21407	73	31	42.4658	41	15	36.5854		
4	PLA	RESPBPRS	LVCF	0.28512	0.13993	0.5810	0.00055	112	34	30.3571	115	17	14.7826	*	
5	PLA	RESPFI	OBSERVED CASES	0.95408	0.41226	2.2080	0.91256	66	33	50.0000	49	28	57.1429		
6	PLA	RESPFI	LVCF	0.62615	0.33711	1.1630	0.13836	95	41	43.1579	108	43	39.8148		
7	PLA	RESPFV	OBSERVED CASES	0.58365	0.25353	1.3436	0.20562	68	38	55.8824	48	22	45.8333		
8	PLA	RESPFV	LVCF	0.32391	0.17223	0.6092	0.00047	106	45	42.4528	120	30	25.0000	*	
9	PLA	RESPHOST	OBSERVED CASES	3.05269	0.87224	10.6838	0.08079	39	18	46.1538	26	17	65.3846		
10	PLA	RESPHOST	LVCF	0.54936	0.25287	1.1935	0.13024	64	30	46.8750	66	26	39.3939		
11	PLA	RESPJMCK	OBSERVED CASES	0.78544	0.34015	1.8136	0.57163	73	41	56.1644	46	25	54.3478		
12	PLA	RESPJMCK	LVCF	0.37059	0.20183	0.6805	0.00137	113	47	41.5929	121	32	26.4463	*	
13	PLA	RESPMOOD	OBSERVED CASES	0.94119	0.39114	2.2647	0.89238	73	35	47.9452	45	27	60.0000		
14	PLA	RESPMOOD	LVCF	0.43121	0.22746	0.8175	0.00995	104	42	40.3846	116	38	32.7586	*	
15	HAL	RESPANX	OBSERVED CASES	1.29289	0.75330	2.2190	0.35129	122	58	47.5410	131	78	59.5420		
16	HAL	RESPANX	LVCF	0.94565	0.61323	1.4582	0.80034	179	68	37.9888	229	99	43.2314		
17	HAL	RESPBPRS	OBSERVED CASES	1.04852	0.64126	1.7144	0.85019	139	70	50.3597	164	96	58.5366		
18	HAL	RESPBPRS	LVCF	0.96270	0.64271	1.4420	0.85372	196	72	36.7347	262	107	40.8397		
19	HAL	RESPFI	OBSERVED CASES	0.99822	0.59598	1.6719	0.99461	117	61	52.1368	151	83	54.9669		
20	HAL	RESPFI	LVCF	0.83100	0.55084	1.2537	0.37756	169	72	42.6036	260	106	40.7692		
21	HAL	RESPFV	OBSERVED CASES	1.16281	0.68557	1.9723	0.57577	132	80	60.6061	168	118	70.2381		
22	HAL	RESPFV	LVCF	1.20884	0.81128	1.8012	0.35127	194	89	45.8763	262	145	55.3435		
23	HAL	RESPHOST	OBSERVED CASES	0.86477	0.33671	2.2210	0.76272	52	34	65.3846	61	43	70.4918		
24	HAL	RESPHOST	LVCF	0.94621	0.47459	1.8865	0.87519	84	48	57.1429	94	59	62.7660		
25	HAL	RESPJMCK	OBSERVED CASES	0.97707	0.58892	1.6211	0.92845	135	78	57.7778	163	102	62.5767		
26	HAL	RESPJMCK	LVCF	0.84429	0.56630	1.2587	0.40617	193	84	43.5233	264	117	44.3182		
27	HAL	RESPMOOD	OBSERVED CASES	1.07406	0.64692	1.7832	0.78238	122	59	48.3607	151	82	54.3046		
28	HAL	RESPMOOD	LVCF	0.85891	0.57051	1.2931	0.46624	174	70	40.2299	262	104	39.6947		
29	CHL	RESPANX	OBSERVED CASES	0.85243	0.45192	1.6079	0.62191	79	47	59.4937	86	49	56.9767		
30	CHL	RESPANX	LVCF	0.97007	0.56382	1.6690	0.91260	97	49	50.5155	120	60	50.0000		
31	CHL	RESPBPRS	OBSERVED CASES	1.03509	0.56713	1.8892	0.91054	90	48	53.3333	109	62	56.8807		
32	CHL	RESPBPRS	LVCF	0.91834	0.54623	1.5439	0.74791	108	51	47.2222	148	70	47.2973		
33	CHL	RESPFI	OBSERVED CASES	0.82522	0.39631	1.7183	0.60770	66	47	71.2121	70	47	67.1429		
34	CHL	RESPFI	LVCF	0.83306	0.45998	1.5087	0.54668	83	49	59.0361	98	53	54.0816		
35	CHL	RESPFV	OBSERVED CASES	1.78671	0.93059	3.4304	0.08119	78	44	56.4103	100	72	72.0000		
36	CHL	RESPFV	LVCF	1.43833	0.84486	2.4487	0.18057	97	46	47.4227	142	83	58.4507		
37	CHL	RESPHOST	OBSERVED CASES	1.24363	0.48324	3.2005	0.65120	43	31	72.0930	56	42	75.0000		
38	CHL	RESPHOST	LVCF	1.15565	0.55359	2.4125	0.70006	52	33	63.4615	85	55	64.7059		

39	CHL	RESPJMCK	OBSERVED CASES	1.65117	0.86943	3.1358	0.12542	85	49	57.6471	99	70	70.7071		
40	CHL	RESPJMCK	LVCF	1.34230	0.79542	2.2652	0.27018	102	50	49.0196	141	81	57.4468		
41	CHL	RESPMOOD	OBSERVED CASES	0.86268	0.42215	1.7629	0.68541	69	48	69.5652	81	55	67.9012		
42	CHL	RESPMOOD	LVCF	1.15954	0.65175	2.0630	0.61456	88	49	55.6818	112	66	58.9286		
43	RIS	RESPANX	OBSERVED CASES	3.88134	1.37216	10.9789	0.01058	24	10	41.6667	64	45	70.3125	*	
44	RIS	RESPANX	LVCF	2.13994	0.88505	5.1741	0.09123	30	11	36.6667	94	50	53.1915		
45	RIS	RESPBPRS	OBSERVED CASES	7.78886	3.18149	19.0685	0.00001	33	11	33.3333	87	69	79.3103	*	
46	RIS	RESPBPRS	LVCF	5.11447	2.28449	11.4501	0.00007	38	11	28.9474	111	75	67.5676	*	
47	RIS	RESPFI	OBSERVED CASES	3.06761	1.21658	7.7349	0.01753	29	13	44.8276	60	43	71.6667	*	
48	RIS	RESPFI	LVCF	2.07549	0.91839	4.6904	0.07920	33	14	42.4242	90	55	61.1111		
49	RIS	RESPFV	OBSERVED CASES	7.49615	2.78970	20.1428	0.00006	29	14	48.2759	82	72	87.8049	*	
50	RIS	RESPFV	LVCF	3.27074	1.46442	7.3051	0.00385	33	14	42.4242	113	80	70.7965	*	
51	RIS	RESPHOST	OBSERVED CASES	0.85487	0.08322	8.7819	0.89504	6	5	83.3333	32	26	81.2500		
52	RIS	RESPHOST	LVCF	0.45404	0.04884	4.2213	0.48764	7	6	85.7143	41	30	73.1707		
53	RIS	RESPJMCK	OBSERVED CASES	8.23135	3.24559	20.8761	0.00001	33	14	42.4242	85	73	85.8824	*	
54	RIS	RESPJMCK	LVCF	4.16116	1.91339	9.0495	0.00032	38	14	36.8421	113	80	70.7965	*	
55	RIS	RESPMOOD	OBSERVED CASES	3.01674	1.19839	7.5941	0.01907	28	13	46.4286	72	53	73.6111	*	
56	RIS	RESPMOOD	LVCF	1.90436	0.85426	4.2453	0.11529	33	14	42.4242	104	62	59.6154		

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	1.07810	0.71502	1.62556	0.71964	201	105	52.2388	217	127	58.5253	
2	PLA	RESPANX	LVCF	0.94935	0.67727	1.33075	0.76292	276	117	42.3913	349	159	45.5587	
3	PLA	RESPBPRS	OBSERVED CASES	1.04969	0.71774	1.53517	0.80255	229	118	51.5284	273	158	57.8755	
4	PLA	RESPBPRS	LVCF	0.95217	0.69252	1.30918	0.76289	304	123	40.4605	410	177	43.1707	
5	PLA	RESPFI	OBSERVED CASES	0.94098	0.61739	1.43419	0.77725	183	108	59.0164	221	130	58.8235	
6	PLA	RESPFI	LVCF	0.82950	0.59196	1.16237	0.27751	252	121	48.0159	358	159	44.4134	
7	PLA	RESPFV	OBSERVED CASES	1.40105	0.93230	2.10550	0.10466	210	124	59.0476	268	190	70.8955	
8	PLA	RESPFV	LVCF	1.28047	0.93198	1.75928	0.12717	291	135	46.3918	404	228	56.4356	
9	PLA	RESPHOST	OBSERVED CASES	1.03770	0.53400	2.01653	0.91305	95	65	68.4211	117	85	72.6496	
10	PLA	RESPHOST	LVCF	1.04078	0.62963	1.72042	0.87614	136	81	59.5588	179	114	63.6872	
11	PLA	RESPJMCK	OBSERVED CASES	1.20292	0.81050	1.78536	0.35910	220	127	57.7273	262	172	65.6489	
12	PLA	RESPJMCK	LVCF	0.99858	0.72775	1.37018	0.99297	295	134	45.4237	405	198	48.8889	
13	PLA	RESPMOOD	OBSERVED CASES	1.00575	0.66620	1.51835	0.97823	191	107	56.0209	232	137	59.0517	
14	PLA	RESPMOOD	LVCF	0.94434	0.67704	1.31716	0.73585	262	119	45.4198	374	170	45.4545	

Technical Document (TD004)

Approved for issue by:

Andrew Gorman
Project Team Physician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

Emma Westhead
Senior Statistician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

EXHIBIT 20

1) angioedema
2) ~~Lmited~~
3) hyperglyc, diabetes

DISCUSSION DOCUMENT

US - involuntary movements
CDS - discussion

SEROQUEL™

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

6 cases
median time to onset new diabetes 0.5 mos.

Wayne
PB 2240
base rates

gov't

Emma, MJ - dose response
Geoff - 6 cases, conclusions

Lumy CDS in line w US PT's

CONCLUSION: KEEP ISSUE UNDER REVIEW

AUTHOR(S):

Wayne K. Geller MD
Medical Director, Drug Safety
Wilmington, DE

SIGNATURE: .....

DATE: .....

of 10 cases from clinical trials → each source?

 RIS labelled for diabetes, DKA

SUMMARY AND CONCLUSIONS:

Presently, the SEROQUEL Core Data Sheet (CDS) does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with SEROQUEL therapy. Safety data derived from clinical trials and spontaneous reports, despite often containing limited information, suggest the possibility of an association between SEROQUEL use and impaired glucose regulation including occasional reports of new onset diabetes mellitus. While none of these reports are absolutely steadfast, the number of reports is fairly sizeable. Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis. While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

1 INTRODUCTION

criteria used in this assessment: FBS 7126, 2hr post 75gm 7200

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for SEROQUEL and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for SEROQUEL for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The SEROQUEL core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with SEROQUEL:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The SEROQUEL US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels $\geq$110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

(1) Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or

(2) Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or

(3) Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with
Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:

Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)

- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12 to 16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

(1) The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).

(2) Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

16 spont
no attributes ← 10 clin trials
2 lit reports

Clozapine: *Warnings and Precautions*:

Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases.

9 cases new onset

Case Number: 2000UW01164

4 DKA, 2 new onset
2 unsure

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

NKHOC - 0

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started SEROQUEL 200 mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on SEROQUEL. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving SEROQUEL, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving SEROQUEL 300 mg daily since 06 December 1999. On 26 January 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. SEROQUEL was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include zoloft, klonopin, haldol and depakote.

Follow-up 23 February 2000: Pharm D reports that "after further testing, the attending physicians did not feel that SEROQUEL was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving SEROQUEL and developed diabetes. Physician feels that SEROQUEL may possibly be responsible for the development of diabetes.

Follow-up 11 November 1999: Physician reports that the 47 year old female (not 45) had been receiving SEROQUEL 600 mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. SEROQUEL was tapered for discontinuation. Concomitant medications include klonopin and benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "SEROQUEL caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS

A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving SEROQUEL 100 mg every evening since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of SEROQUEL was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 September 1999, SEROQUEL dosage was again decreased to 25 mg every evening. The patient had been receiving risperidol prior to

SEROQUEL. Concomitant medications include ritalin for attention disorder and serzone for depression.

Case Number: 1999UW00969

COMPLICATIONS OF DIABETES MELLITUS

A report has been received from a physician concerning a 28 year old male patient who was taking SEROQUEL and lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14 March 1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.

*Follow-up received 22 March 1999: A pharmacist reports that the patient started zithromax on 10 March 1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14 March 1999: The patient presented on 14 March 1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15 March 1999. The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05 May 1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10 to 16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967

DIABETES

A report has been received from a physician concerning a 17 year old male who is receiving SEROQUEL 200 mg twice daily for schizophrenia. The patient was initially started on 100 mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300 mg daily. Patient also receives paxil and depakote. Patient continues on SEROQUEL.

Case Number: 1999UW00288

BLOOD SUGAR RISING

A report has been received from a 58-year-old diabetic female patient who has been receiving SEROQUEL since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 January 1999 the reading was 321.

Case Number: 1999AP06660

LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA

A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving SEROQUEL since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300 to 400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started SEROQUEL in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control, particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5 mg/day. At the time of reporting the events were ongoing.

The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757

DIABETES, KETOACIDOSIS.

A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750 mg daily for psychosis since November 1997. He was receiving acamprosate, depixol and priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.

The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218

DIABETES DURING PREGNANCY

Patient developed diabetes during pregnancy and started insulin on 30 September 1999. Baby due 06 December 1999, but patient's water broke 30 September 1999 and baby born in October 1999. See case 1999AP06076.

Case Number: 1999AP02989

DIABETES MELLITUS

This patient started treatment with SEROQUEL on 13 November 1998 and with fluoxetine on 12 November 1998. Urine and blood tests on 26 November 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985

NON INSULIN DEPENDENT DIABETES

A physician reported that a 44 year male patient was given SEROQUEL 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting SEROQUEL, the patient developed non-insulin dependent diabetes. SEROQUEL was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554

CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.

A report has been received from a physician concerning a 58 year old male patient who received SEROQUEL 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081

HYPERGLYCAEMIA

Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 1998. Open label medication started on 14 September 1998 and ended on 26 September 1998. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844

HYPERGLYCAEMIA, DIABETES.

A report has been received from a physician concerning a male patient in his early forties who has been receiving SEROQUEL for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.

NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken SEROQUEL since July 1998. On 31 August 1998 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 October 1999: Further information reveals that the patient was receiving SEROQUEL 200 mg for a bipolar disorder since July 1998. On 31 August 1999, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. SEROQUEL was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408

HYPERGLYCAEMIA (NON-SERIOUS)

A pharmacist and a nurse reported that a male patient taking SEROQUEL developed hyperlycaemia. The pharmacist considered the event unrelated to SEROQUEL; the nurse considered the event related to SEROQUEL. The patient was also taking stelazine.

Case Number: 1998AP45979

LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR

Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with SEROQUEL, SEROQUEL dosage has been reduced from 400 to 200mg. The physician is thinking of stopping SEROQUEL altogether.

Case Number: 1998AP18089

HYPERGLYCAEMIA.

A report has been received from a physician concerning a 32 year old male patient who has been receiving SEROQUEL from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.

On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803

DIABETIC KETOACIDOSIS

A report has been received from a physician concerning a 36 year old male who has been receiving SEROQUEL in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. SEROQUEL started on 06 September 1996. The patient had recently been diagnosed with diabetes mellitus which was controlled on glucotrol. On 18 March 1997, 28 weeks after starting SEROQUEL, he was admitted to hospital with decreased level of consciousness. He had not been taking his glucotrol or SEROQUEL for 3 to 4 days prior to admission. He was given IV fluids and insulin but later developed severe acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were:

sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin and food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted SEROQUEL. The event resolved on 01 April 1997. The investigator felt that there was not a reasonable possibility that the event was related to SEROQUEL.

Case Number: 1997AP36246

UNCONTROLLED DIABETES

A report has been received from a physician concerning a 29-year old male who has been receiving SEROQUEL since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. SEROQUEL treatment was put on hold and the patients diabetes treated with humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the SEROQUEL therapy.

Case number: 1997AP35710

UNCONTROLLED DIABETES MELLITUS

A report has been received regarding a 45 year old male who has been receiving SEROQUEL as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 August 1997, 163 days after starting SEROQUEL, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.

The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874

PNEUMONIA, DIABETES, HYPERTENSION

This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with SEROQUEL as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.

The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737

DIABETES MELLITUS

This 52 year-old-female with schizophrenia was taking SEROQUEL 400 mg from 28 January 1995 as part of a clinical trial. On 31 January 1995 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April 1995, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.

This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544

AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in SEROQUEL trial on 26 September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4 November, the patient developed

symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with SEROQUEL.

Case Number: 1994AP03286

HYPERGLYCAEMIA

An investigator reported that a 53 year old female patient started taking SEROQUEL on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893

HYPERGLYCAEMIA

An investigator reported that a 45 year old male was treated with SEROQUEL beginning on 4 March 1994. Concomitant medications included zantac and haldol. The patient had no history of diabetes mellitus. He had recently stopped taking an unblinded SEROQUEL study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. SEROQUEL was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5 DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of pre-existing diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of pre-existing diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to SEROQUEL.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily SEROQUEL dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months

(median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily SEROQUEL dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to 21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking SEROQUEL 150 mg daily for 30 months. The latter report contains scant information, except the daily SEROQUEL dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient

Note Wayne impressed by 2 physicians noting ~~dose~~ diabetes onset with dose increase.

developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

6 REFERENCES

(1) Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

(2) American Diabetes Association: Clinical Practice Recommendations 2000, Volume 23 Supplement 1, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

(3) Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

(4) Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

Usually no baseline fasting glucose
7 had taking decrep assoc w diabetes
Some reports - scant info
No + de or re challenge

Seroquel may cause impaired glucose regulation in some individuals.
No ~~of~~ signal of Type 1 ie no negative impact on insulin production

DISCUSSION
No + re, de challenge
No bsl CHO
low # of cases for a common condition
No mechanism of effect

For my part of 4 cases, DKA speaks to absence of dechallenge effect.

other pts
1. will get long term data from okay trial
2. will know more after response to FDA concludes

EXHIBIT 21

ACCESSION NUMBER:

SAFETY POSITION PAPER

'SEROQUEL'

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

AUTHOR:
Wayne K. Geller, MD
Global Drug Safety Physician
Wilmington, DE

SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

Currently, the Seroquel CDS does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with Seroquel therapy. Safety data derived from clinical trials and spontaneous reports often containing limited information may represent a weak signal linking Seroquel with impaired glucose regulation, including occasional reports of new onset diabetes mellitus. None of these reports are absolutely steadfast (i.e., there are no clear index cases and there were no reports of positive dechallenges/rechallenges) and most have either incomplete information or other explainable causes. Although the number of reports is fairly sizable, it was felt that there is insufficient evidence at present to warrant an amendment to the Seroquel CDS. However, it was agreed that this topic will be kept under ongoing review and will be reassessed at a later time. Additional clinical trials are planned in which baseline fasting blood glucose concentrations will be obtained as well as follow-up measurements on study drug.
Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis.

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for Seroquel and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for Seroquel for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The Seroquel core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with Seroquel:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The Seroquel US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

1. Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or
2. Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or
3. Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:
Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)
- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12-16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

1. The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).
2. Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:
Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on Clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with Seroquel. The following are narratives for these 28 cases.

Case Number: 2000UW01164

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include Zoloft, Klonopin, Haldol and Depakote. Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes. Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS
A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving Seroquel 100mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

Case Number: 1999UW00969
COMPLICATIONS OF DIABETES MELLITUS
A report has been received from a physician concerning a 28 year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14-Mar-1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.
*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.
*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15-Mar-1999. The reporter attributed the event to a drug effect from multiple prescriptions.
*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10-16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967
DIABETES
A report has been received from a physician concerning a 17 year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with Glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Case Number: 1999UW00288
BLOOD SUGAR RISING
A report has been received from a 58-year-old diabetic female patient who has been receiving Seroquel since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 Jan 99 the reading was 321.

Case Number: 1999AP06660
LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA
A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving Seroquel since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300-400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started Seroquel in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control,

particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5mg/day. At the time of reporting the events were ongoing.
The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757
DIABETES, KETOACIDOSIS.
A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.
The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218
DIABETES DURING PREGNANCY
Patient developed diabetes during pregnancy and started insulin on 30 Sept 99. Baby due 06 December 1999, but patient's water broke 30 Sept 99 and baby born in Oct 99. See case 1999AP06076.

Case Number: 1999AP02989
DIABETES MELLITUS
This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985
NON INSULIN DEPENDENT DIABETES
A physician reported that a 44 year male patient was given Seroquel 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting Seroquel, the patient developed non-insulin dependent diabetes. Seroquel was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554
CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.
A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081
HYPERGLYCAEMIA
Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 98. Open label medication started on 14 September 98 and ended on 26 September 98. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844
HYPERGLYCAEMIA, DIABETES.
A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.
NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512
DIABETES MELLITUS
A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.
*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 99, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.
SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408
HYPERGLYCAEMIA (NON-SERIOUS)
A pharmacist and a nurse reported that a male patient taking Seroquel developed hyperlycaemia. The pharmacist considered the event unrelated to Seroquel; the nurse considered the event related to Seroquel. The patient was also taking Stelazine.

Case Number: 1998AP45979
LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR
Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with Seroquel, Seroquel dosage has been reduced from 400 to 200mg. The physician is thinking of stopping Seroquel altogether.

Case Number: 1998AP18089
HYPERGLYCAEMIA.
A report has been received from a physician concerning a 32 year old male patient who has been receiving Seroquel from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.
On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803
DIABETIC KETOACIDOSIS
A report has been received from a physician concerning a 36 year old male who has been receiving Seroquel in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. Seroquel started on 06 Sept 96. The patient had recently been diagnosed with diabetes mellitus which was controlled on Glucotrol. On 18 March 97, 28 weeks after starting Seroquel, he was admitted to hospital with decreased level of consciousness. He had not been taking his Glucotrol or Seroquel for 3-4 days prior to admission. He was given IV fluids and insulin but later developed severe

acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were: sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin & food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted Seroquel. The event resolved on 01 April 97. The investigator felt that there was not a reasonable possibility that the event was related to Seroquel.

Case Number: 1997AP36246
UNCONTROLLED DIABETES
A report has been received from a physician concerning a 29-year old male who has been receiving Seroquel since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. Seroquel treatment was put on hold and the patients diabetes treated with Humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the Seroquel therapy.

Case number: 1997AP35710
UNCONTROLLED DIABETES MELLITUS
A report has been received regarding a 45 year old male who has been receiving Seroquel as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 Aug 97, 163 days after starting Seroquel, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.
The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874
PNEUMONIA, DIABETES, HYPERTENSION
This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with Seroquel as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.
The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737
DIABETES MELLITUS
This 52 year-old-female with schizophrenia was taking Seroquel 400 mg from 28 January 95 as part of a clinical trial. On 31 January 95 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April '95, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.
This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544
AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in Seroquel trial on 26th September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4th November, the patient developed symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with Seroquel.

Case Number: 1994AP03286
HYPERGLYCAEMIA
An investigator reported that a 53 year old female patient started taking Seroquel on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893
HYPERGLYCAEMIA
An investigator reported that a 45 year old male was treated with Seroquel beginning on 4 March 1994. Concomitant medications included Zantac and Haldol. The patient had no history of diabetes mellitus. He had recently stopped taking a n unblinded Seroquel study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. Seroquel was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5 DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of preexisting diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of preexisting diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to Seroquel.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily Seroquel dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months (median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to

21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking Seroquel 150 mg daily for 30 months. The latter report contains scant information, except the daily Seroquel dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet based upon postmarketing and clinical trial safety data.

6 REFERENCES

[1] Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

[2] American Diabetes Association: Clinical Practice Recommendations 2000, Volume 23 Supplement 1, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

[3] Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

[4] Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

EXHIBIT 22

Unknown

From: Wayne Geller
Sent: Monday, September 18, 2000 6:27 PM
To: G=Dorothee; G=Liz
Cc: G=Safety; G=Joy; G=Vikram
Subject: Re: FW: Quetiapine and glucose metabolism disorders

Attachments: SeroquelSERMDMDKAPositionPaper.doc

Dear Liz and Dorothee,

Attached is a position paper based upon my presentation at the last SERM meeting on diabetes mellitus, diabetic ketoacidosis, and non-ketotic hyperosmolar coma. Please feel free to contact me if you have any additional questions.

Thanks and kind regards,
Wayne

SeroquelSERMDMD
KAPositionPaper...

Thanks,
Wayne

To: Wayne Geller/HQ/Astra Merck
cc: /G=Dorothee/S=Wientjes/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL, /G=Safety/S=Mailbox/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL, /G=Joy/I=JA/S=Gulliford/OU=ALDERLEY/O=PHARMS/P=ZENECA/A=TMAILUK/C=GB
From: Liz Smith @ X400
Date: 09/18/2000 11:51 AM GDT
Subject: FW: Quetiapine and glucose metabolism disorders

Message

Dear Wayne
Please find attached below a request from the Dutch regulatory authorities about Seroquel.
I would be grateful if you could reply direct to Dorothee since I am out of the office after tomorrow, and Mary O'Hare is also out of the office this week.
With many thanks and kind regards,
Liz

From: Wientjens, Dorothee (temp. employee)
Sent: 18 September 2000 08:53
To: Smith, Liz EH
Cc: O'Hare, Mary M; Hyde, Margaret EM; Gulliford, Joy JA; Whittaker, Denise D -

R&D
Subject: FW: Quetiapine and glucose metabolism disorders

Dear Mailbox,

Please find enclosed a letter form the Duth authorities concerningQuetialpine and glucose metabolism.
I would be most grateful if you could address his request.

Thank you in advance

Dorothee PWM Wientjens
DSO
AstraZenecaNL

-----Oorspronkelijk bericht-----
Van: Meiners, dhr. drs. A.P. [mailto:ap.meiners@cbg-meb.nl]
Verzonden: dinsdag 5 september 2000 15:35
Aan: Wientjens Dorothee (temp. employee)
Onderwerp: Quetiapine and glucose metabolism disorders

Dear Dorothee,

At a recent pharmacovigilance working party a signal was raised for one of the other atypical antipsychotic drugs in relation to glucose metabolism disorders. Looking at our recent PSUR assessment reports we don-t seem to have recognised this with Seroquel, however, increases in weight and blood lipids are recognised, so it would not seem impossible. A formal request for an overview and assessment report on all reports of glucose metabolism disorders associated with quetiapine use is coming your way as part of conclusions of assessment of a type II variation application currently under review, but to expedite matters I am also already sending you this request by e-mail. Would it be possible to submit such a report on short notice. It probably doesn-t have to be very extensive as it only focusses on a single issue and it could well be that the number of reports is very limited(even if it would require searching your database for terms such as glucose metablism disorder, glucose incresased, hyperglycemia, diabetes, hypoglycemia, etc.)

Sincerely,
==========
Arthur P. Meiners, head of pharmacovigilance
Medicines Evaluation Board
Kalvermarkt 53 PoBox 16229
2500 BE The Hague
Netherlands
tel +31(70)3567492
fax +31(70)3567515
mailto:ap.meiners@cbg-meb.nl

EXHIBIT 23

From: Wientjens, Dorothee (temp. employee)
Sent: Tuesday, October 03, 2000 3:20 PM
To: Geller, Wayne
Subject: RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for yoy fax, which I sent to the local authorities.

Best regards,

Drothee PWM WIentjens
DSO
AstraZenecaNL

-----Oorspronkelijk bericht-----
Van: Geller Wayne
Verzonden: maandag 25 september 2000 22:38
Aan: Wientjens Dorothee (temp. employee); Schotel Luci
Onderwerp: RE: Quetiapine and glucose metabolism disorders

Hi Dorothee,

The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once.

Thanks,
Wayne

-----Original Message-----
From: Wientjens, Dorothee (temp. employee)
Sent: Monday, September 25, 2000 5:16 AM
To: Geller, Wayne
Subject: RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

I think it is ok to send me a hard copy by mail. Then I will send it to the authoroties. From tuesday onwards I will be at a conference, so please contact Luci Schotel, our secretary.

Thank you in anticipation.

Dorothee

-----Oorspronkelijk bericht-----
Van: Geller Wayne
Verzonden: vrijdag 22 september 2000 18:25
Aan: Wientjens Dorothee (temp. employee)
Onderwerp: RE: Quetiapine and glucose metabolism disorders
Urgentie: Hoog

Hi Dorothee,

I spoke with our information services department, and it appears that I can not send you a signed PDF-file electronically as you requested. Do you have time for me to send this either as a fax or a signed hard copy?

Please advise. I will not be in the office Monday.

Thanks,

Wayne

-----Original Message-----
From: Wientjens, Dorothee (temp. employee)
Sent: Friday, September 22, 2000 11:51 AM
To: Geller, Wayne
Subject: Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for the safety position paper on seroquel. Would you be so kind as to send me the front page of the paper (as a PDF-file) with your signature and date of report, so I can send it to the local authorities.

Thank you in anticipation

Dorothee P.W.M. Wientjens
dso
Astra ZenecaNL

EXHIBIT 26

Id : i.m.42d9083b5f5fe9dd9720b05f6052ad5b
CN : SQ1ED00428632
Date : Tuesday, October 31, 2000 7:20:00 AM GMT
From : Witch, Emma
To : Haas, Edward J
Cc : Geller, Wayne
Subject : RE: Urgent--Request for Seroquel document re Diabetes sent to FDA
Attachments : final document 280800.doc
Custodians : Geller, Wayne

From:
Witch, Emma

Sent:
Tuesday, October 31, 2000 8:25 AM

To:
Haas, Edward J

Cc:
Geller, Wayne

Subject:
RE: Urgent--Request for Seroquel document re Diabetes sent to FDA

Attachments:
final diabetes document 280800

Hi there

CONFIDENTIAL

Here is the diabetes doc that went to the FDA.

Regards

Emma

From: Haas, Edward J

Sent: 30 October 2000 22:50

To: Witch, Emma

Cc: Geller, Wayne

Subject: Urgent--Request for Seroquel document re Diabetes sent to FDA

Hello Emma,

Can you please provide me and Wayne wth a copy of the document that was sent to the FDA regarding diabetes. Thank you very much!

Ed

cid:CHILKAT-CID-469c0a8d-8b33-4364-90d9-a7d90f0ecb84

SEROQUEL™ (quetiapine fumarate)

Response to FDA request for further safety information

To assess the possibility of a causal association between Seroquel treatment and disturbances in glucose regulation

NDA 20-639

August 2000

CONTENTS PAGE

1 INTRODUCTION

The purpose of this document is to provide the FDA with further safety information in order to assess whether there is a causal association between Seroquel treatment and disturbances in glucose regulation, in particular the onset of diabetes.

The FDA have requested 6 pieces of information; these are summarized as follows:

(1) A comprehensive review of all preclinical data pertaining to hyperglycemia.

(2) A thorough assessment of all Phase 1, 2 and 3 studies in the Seroquel NDA for evidence of adverse events possibly related to disturbances in glucose regulation, mean changes from baseline in plasma glucose levels, and the number of patients meeting the criteria for a markedly abnormal plasma glucose concentration.

(3) A review of spontaneous postmarketing reports for new-onset diabetes, hyperosmolar coma, diabetic ketoacidosis, weight gain and hyperglycemia.

(4) An estimate of patient exposure.

(5) Copies of any correspondence with regulatory authorities regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

(6) The possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

AstraZeneca has now collated and thoroughly assessed all the appropriate data to address each of the above, and full details are provided in this document (Sections 4 to 9).

A summary of preclinical, clinical and postmarketing findings, and an overall conclusion, is provided overleaf.

2 SUMMARY OF DATA

Preclinical data

- A review of all the preclinical data has confirmed that the only salient observations are small changes in glucagon secreting cells in a 1-year rat study with quetiapine fumarate.

  No such changes were observed after administration of quetiapine fumarate at the same dose levels for 2 years in another rat study. Further, no such changes were observed in any of the other species tested in the preclinical program, and no changes in serum glucose levels or pathology indicative of a diabetic condition were observed throughout the preclinical toxicology program.

  Thus the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in man.

  Overall it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

Clinical data

- The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies and, after adjusting for time-on-study, the incidence of these events did not increase as the duration of exposure to Seroquel increased:
  - cumulative incidence: 1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials (≤ 6 weeks duration), 4.6% in the long-term controlled (> 6 weeks duration) and 3.6% in the uncontrolled trials.
  - incidence density (events/patient-years): 0.6 in the Phase I trials, 0.2 in the short-term controlled trials, 0.2 in the long-term controlled trials and 0.1 in the uncontrolled trials.
- None of the 2419 patients exposed to Seroquel in the clinical trial program were reported as having diabetic ketoacidosis or hyperosmolar coma.
- Only 3 of 2419 patients (0.1%) were reported as having diabetes mellitus (all in the uncontrolled trials). In 2 of the 3 cases, the patients had a past history of diabetes. In the third case, the patient is reported to have 'recovered' from diabetes and continued treatment with Seroquel.

- The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (67 of 2419 patients, 2.8%).

Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program also had diabetes mellitus recorded as an adverse event. This patient had diabetes at baseline (for which they were receiving treatment) and the adverse event of 'poorly controlled diabetes' was subsequently reported.

- There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due to events possibly related to glucose dysregulation; details are as follows:

  - 2 patients were withdrawn for hyperglycemia in the uncontrolled trials. In both cases, the hyperglycemia was considered serious by the Investigator. Both patients had baseline confounding factors: 1 was a known diabetic with a history of hyperglycemia and 1 had a history of borderline glucose levels.

  - 1 patient was withdrawn for weight gain in the short-term controlled trials. The weight gain was not considered serious by the Investigator. Somnolence and abdominal distension were also documented as reasons for withdrawal from treatment in this patient.

  Apart from the 2 adverse events of hyperglycemia above, none of the other events possibly related to disturbances in glucose regulation in the NDA clinical trial program were considered serious by the Investigator.

- There were no statistically significant differences between the Seroquel and placebo groups, Seroquel and chlorpromazine groups (short-term trials) or Seroquel and haloperidol groups (long-term trials) in the mean change from baseline to end of treatment in plasma glucose levels.

- The number of patients treated with Seroquel with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (3.4% in the short-term trials [≤ 6 weeks duration] and 2.9% in the long-term trials [> 6 weeks duration]).

- Where hyperglycemia was observed (glucose value ≥ 200 mg/dl), the condition was not sustained or extreme, and the patients were asymptomatic.

Postmarketing data

- It is estimated that over 623,000 patients have been exposed to Seroquel since its launch in the US in 1997. During this time:
  - no cases of hyperosmolar coma have been reported.
  - 3 cases of diabetic ketoacidosis have been reported. In 2 cases, usage of concomitant medications known to impair glucose tolerance was noted.
  - 12 cases of new-onset diabetes have been reported. In 6 patients, usage of concomitant medications known to impair glucose tolerance was noted.
  - 2 cases of hyperglycemia have been reported.
  - 38 cases of weight gain were reported. Only 2 of the 38 patients with weight gain also had diabetes mellitus.

  Thus very few cases of diabetes mellitus (and related complications), hyperglycemia, and weight gain have been reported. AstraZeneca believes that the current US Seroquel label accurately describes patient experiences to date of these conditions.

3 CONCLUSION

The preclinical data has provided no evidence that Seroquel treatment in man may be associated with diabetes.

The clinical data has shown that the incidence of adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel is low and does not increase as duration of exposure to Seroquel increases. Very few of the adverse events observed were considered serious or led to withdrawal of treatment. There were no cases of diabetic ketoacidosis or hyperosmolar coma and only 3 cases of diabetes mellitus were reported.

A review of the plasma glucose data has revealed similar findings: the hyperglycemia (glucose value ≥ 200 mg/dl) observed in a small number of patients treated with Seroquel was not sustained, extreme, or associated with any symptoms. Further, the incidence of hyperglycemia did not increase as the duration of exposure to Seroquel increased. In addition, there were no statistically significant differences between Seroquel and placebo in the mean changes from baseline to endpoint in plasma glucose levels.

The postmarketing data has shown that even though over 600,000 patients are estimated to have received Seroquel, the number of reported cases of diabetes and related conditions has been extremely small.

Overall, following extensive reviews of all the preclinical, clinical, and postmarketing data, AstraZeneca believes that a diabetogenic potential for Seroquel is unlikely.

4 REVIEW OF PRECLINICAL DATA

In response to Part 1 of the FDA's request, AstraZeneca has completed a comprehensive review of all the preclinical data for evidence of an association between quetiapine fumarate treatment and disturbances in glucose metabolism.

4.1 Salient observations

Hyperplasia of small glucagon secreting cells (alpha cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day dose groups following administration of quetiapine for 12 months to rats (TFR/1626). The changes observed were minimal in severity and were not observed after administration for 2 years at the same dose levels in another rat study (TCR/1624).

No such changes were observed in the pancreatic islets of mice, dogs or primates during single- or multiple- dose studies (of up to 12 months duration) with quetiapine fumarate. In addition, no consistent changes in blood glucose levels occurred during any toxicology study in any species. Further, throughout all the extensive preclinical toxicity studies, there was no degenerative pathology that would reflect the induction of a diabetic state.

4.2 Discussion

A functional change in pancreatic islets might be an expected consequence of administration of a dopamine receptor antagonist that increases circulating prolactin. The lactogenic hormones can modulate pancreatic islet beta-cell function (Landgraf et al 1977, Nielsen JH et al 1982, Michaels RL et al 1987); prolactin stimulates an increase in islet cell protein synthesis leading to an increased secretion of insulin (Markoff et al 1990). Conversely, dopamine agonists decrease the glucose-stimulated release of insulin from beta-cells (Morricone et al 1990, Cavaziel et al 1981). The major physiological importance of glucagon (from alpha-cells) relates to its involvement in metabolic control, where its actions generally oppose that of insulin (Unger et al 1981). Because of its close interrelationship with insulin, many of the drugs that affect beta-cells and insulin also produce effects on alpha cells and glucagon (Woodman 1997).

The above observations in the rat study, together with the literature reports of the effects of dopamine antagonists, would suggest that there is a possibility of quetiapine fumarate affecting islet cell homeostasis. However, no such findings were observed in any of the other species in the toxicology program, and no glucose changes or pathology indicative of a diabetic condition was observed throughout the preclinical program. Thus the hyperplasia of glucagon secreting cells observed in the single rat study appears to be of little or no pathologic consequence and thus does not have the potential for clinical significance.

4.3 Conclusion

A review of all the preclinical data has confirmed that the only salient observations are the small changes in glucagon secreting cells in a 1-year rat study with quetiapine fumarate. This observation is considered to be of minimal pathological significance and would not be expected to have any clinical significance in man.

Overall it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

5 REVIEW OF CLINICAL DATA

In response to Part 2 of the FDA's request, AstraZeneca has thoroughly reviewed the clinical safety database in the Seroquel NDA for evidence of an association between Seroquel treatment and disturbances in glucose metabolism.

5.1 Source material

5.1.1 Adverse event data

In the Seroquel NDA, adverse events were categorized using an in-house dictionary based on the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). For the purpose of this review, a list of COSTART terms for adverse events that could be related to disturbances in glucose metabolism has been identified, and are as follows:

thirst, polyuria, urinary frequency, weight gain, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, hyperosmolar coma

The incidence of the above events in all of the patients in the Seroquel NDA clinical trial program has been reviewed and assessed in this report. The number of patients exposed to treatment in the Seroquel NDA clinical trial program is presented in Table 1.

Table 1 Summary of clinical trials in the Seroquel NDA integrated database

Pools by trial design	Treatment group and number of patients			
	Seroquel	Placebo	Haloperidol	Chlorpromazine
Phase I	300	0	0	0
Controlled Phase II/III	1710	206	320	100
Short-term (≤ 6 weeks duration)	1450	206	279	100
Long-term (> 6 weeks duration)	260	0	41	0
Uncontrolled	1256	0	0	0
New exposures	409	0	0	0
Patients already counted under previous headings[a]	847	0	0	0
All trials	**2419**	**206**	**320**	**100**

[a] Previously took part in Phase I or controlled Phase II/III trials

In order to observe the effect of an increased duration of exposure to Seroquel on the incidence of the above adverse events, the adverse data in this report have been divided into the following trial pools:

- Phase I trials
  (Seroquel; N=300)
- Short-term controlled Phase II/III trials
  (≤ 6 weeks duration: Seroquel; N=1450, placebo; N=206, haloperidol; N=279, chlorpromazine; N=100)
- Long-term controlled Phase II/III trials
  (> 6 weeks duration: Seroquel; N =260, haloperidol; N=41)
- Uncontrolled Phase II/III trials
  (Seroquel; N=1256)

As the time-on-study in each treatment group will have varied, overall *incidence density* rates, as well as normal cumulative incidence rates, are presented in this report. (Incidence density is defined as the total number of patients with an event, divided by the total patient year exposure).

5.1.2 Plasma glucose data

In the Seroquel NDA, glucose data were collected in 5 trials: 3 short-term placebo-controlled trials (204636/0008, 5077IL/0004, 5077IL/0006), 1 short-term comparator-controlled trial (204636/0007), and 1 long-term comparator-controlled trial (5077IL/0015).

AstraZeneca has been asked by the Agency to provide details on the mean change from baseline in plasma glucose levels, and the number of patients meeting criteria for a markedly abnormal glucose concentration.

5.1.2.1 Mean change from baseline in plasma glucose levels

Mean changes from baseline to end of treatment in plasma glucose levels have been presented for the following trial pools:

- Short-term placebo controlled trials
  (Seroquel; N=230, placebo; N=143)
- Short-term comparator controlled trials
  (Seroquel; N=93, chlorpromazine; N=92)

- Long-term comparator controlled trials
  (Seroquel N=170, haloperidol; N=35)

To observe any statistically significant differences between the treatment groups in each trial pool, the data were analyzed using analysis of covariance, including the baseline score, treatment, center and center-by-treatment interaction as factors. Differences between the treatments were estimated and 95% confidence intervals and p values have been presented.

5.1.2.2 Number of patients meeting criteria for a markedly abnormal plasma glucose level

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) have defined the diagnostic criteria for diabetes as follows: symptoms of diabetes plus a casual plasma glucose concentration ≥ 200 mg/dl; or a fasting blood glucose level equal to or > 126 mg/dl or a 2-hour blood glucose level ≥ 200 mg/dl during an oral glucose tolerance test (Diabetes Care 1997; 20:1183–1197).

In the Seroquel clinical trials, the Investigators were not instructed when to take plasma samples for assessment of glucose levels, and thus the glucose values obtained were *random* values. Therefore, based on the criteria defined by the Expert Committee above, AstraZeneca has defined a markedly abnormal plasma glucose concentration as ≥ 200 mg/dl, at any time.

The number of patients with a plasma glucose concentration of ≥ 200 mg/dl at any time will be summarized by baseline glucose level, as follows:

- patients with a baseline glucose < 200 mg/dl
- patients with a baseline glucose ≥200 mg/dl
- all patients, irrespective of the baseline value

To observe the effect of an increased during of exposure of trial treatment on the number of patient with a markedly high glucose level, the above data will be summarized in 2 trial pools: short-term trials and long-term trials.

In order to analyze plasma glucose values over the course of treatment, and to obtain details on whether the patients had any symptoms of diabetes, detailed profiles of each patient with a plasma glucose level ≥ 200 mg/dl at any time have been obtained and assessed in this report.

As with the adverse event data, in order to adjust for time-on-study, overall incidence density rates, as well as the normal cumulative incidence rates, will be presented for the proportion of patients with a plasma glucose level ≥ 200 mg/dl at any time.

5.2 Results

5.2.1 Adverse event data

5.2.1.1 Phase I trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the Phase I trials are presented in Table 2.

Table 2 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the Phase I trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=300)
Thirst	0
Polyuria	1 (0.3)
Urinary frequency	2 (0.7)
Weight gain[b]	1 (0.3)
Hyperglycemia	1 (0.3)
Diabetes mellitus	0
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**5 (1.7)**
Total number of events	**5**
Total patient year exposure[c]	**8.0**
Incidence density[d]	**0.6**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Only 5 patients (1.7%) had adverse events possibly related to disturbances in glucose metabolism in the Phase I trials. No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. Urinary frequency was the most commonly reported event in these trials.

None of the events in Table 2 were considered serious by the Investigator, or led to withdrawal from treatment.

5.2.1.2 Controlled Phase II/III trials

(a) Short-term trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the short-term controlled Phase II/III trials (≤ 6 weeks duration) is presented in Table 3.

Table 3 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the short-term controlled Phase II/III trials

COSTART term[a]	Number (%) of patients			
	Seroquel (N=1450)	Placebo (N=206)	Haloperidol (N=279)	Chlorpromazine (N=100)
Thirst	3 (0.2)	0	0	0
Polyuria	1 (<0.1)	0	0	1 (1.0)
Urinary frequency	2 (0.1)	0	1 (0.4)	0
Weight gain[b]	20 (1.4)	0	3 (1.1)	0
Hyperglycemia	0	0	0	0
Diabetes mellitus	0	0	0	0
Diabetic ketoacidosis	0	0	0	0
Hyperosmolar coma	0	0	0	0
Total number of patients with events	**24 (1.7)**	**0**	**4 (1.4)**	**1 (1.0)**
Total number of events	**26**	**0**	**4**	**1**
Total patient year exposure[c]	**119.6**	**14.6**	**24.8**	**9.2**
Incidence density[d]	**0.2**	**0**	**0.2**	**0.1**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Twenty-four patients (1.7 %) treated with Seroquel had adverse events possibly related to disturbances in glucose metabolism in the short-term controlled trials. The incidence density was 0.2, which is similar to that observed in the comparator groups.

Two patients each had 2 events in the Seroquel group; 1 patient had thirst and weight gain, and 1 patient had thirst and polyuria.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. The most frequently reported event in patients treated with Seroquel was weight gain (20 patients, 1.4%); this occurred at a similar incidence as that in the haloperidol group (1.1%).

Of the 20 patients with weight gain in the Seroquel group, 1 patient was withdrawn from treatment due to the weight gain (5077IL/0012/0007/0708). The Investigator did not considered this event to be serious. A review of this patient's details revealed that, in addition to weight gain (2.0 kg over 2 weeks), this patient also withdrew for reasons of somnolence and abdominal distension. A full narrative of this patient is presented in Appendix A.

Apart from the 1 case of weight gain discussed above, none of the other events in Table 3 led to a patient being withdrawn from treatment or were considered serious by the Investigator.

(b) Long-term trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the long-term controlled Phase II/III trials (> 6 weeks duration) is presented in Table 4.

Table 4 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the long-term-controlled Phase II/III trials

COSTART term[a]	Number (%) of patients	
	Seroquel (N=260)	Haloperidol (N=41)
Thirst	1 (0.3)	0
Polyuria	0	0
Urinary frequency	0	0
Weight gain[b]	11 (4.2)	0
Hyperglycemia	0	0
Diabetes mellitus	0	0
Diabetic ketoacidosis	0	0
Hyperosmolar coma	0	0
Total number of patients with events	**12 (4.6)**	**0**
Total number of events	**12**	**0**
Total patient year exposure[c]	**79.3**	**17.6**
Incidence density[d]	**0.2**	**0**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Twelve patients (4.6%) treated with Seroquel had adverse events possibly related to disturbances in glucose metabolism in the long-term controlled trials. The incidence density was 0.2, which is the same as that observed in the short-term trials (Table 3), indicating that the incidence of adverse events possibly related to disturbances in glucose metabolism does not increase as duration of exposure to Seroquel increases.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported in either treatment group. Weight gain was the most frequently reported event in the Seroquel group.

None of the events in Table 4 were considered serious by the Investigator, or led to withdrawal from treatment.

5.2.1.3 Uncontrolled Phase II/III trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the uncontrolled Phase II/III trials are presented in Table 5.

Table 5 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the uncontrolled Phase II/III trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=1256)
Thirst	1 (0.1)
Polyuria	1 (0.1)
Urinary frequency	3 (0.2)
Weight gain[b]	38 (3.0)
Hyperglycemia	2 (0.2)
Diabetes mellitus	3 (0.2)
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**45 (3.6)**
Total number of events	**48**
Total patient year exposure[c]	**386.2**
Incidence density[d]	**0.1**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

In total, 3.6 % of patients had adverse events possibly associated with disturbances in glucose regulation in the uncontrolled trials.

Three patients each had 2 events: 1 patient had hyperglycemia and urinary frequency, 1 patient had thirst and polyuria and 1 patient had diabetes mellitus and weight gain. Weight gain was the most frequently reported event in these trials.

No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Three cases (0.2%) of diabetes mellitus were reported. Full narratives for each patient are presented in Appendix A. In

2 cases (5077IL/0012/0046/4603 and 5077IL/0015/0005/0509), the patients had a history of diabetes. In the final case (5077IL/0014/0036/3605), the patient is reported to have 'recovered' from the diabetes whilst on Seroquel treatment following treatment with glibenclamide. None of the cases of diabetes mellitus were considered by the Investigator to be related to trial therapy. In addition, none of the 3 cases were considered by the Investigator to be serious, or led to withdrawal of treatment.

Two patients had hyperglycemia in these trials. In both cases, the Investigator considered the events to be serious, and the patients were withdrawn from treatment. Full narratives of both patients are presented in Appendix A. Both patients had significant confounding factors: 1 patient (5077IL/0012/0093/9304) had a history of hyperglycemia and diabetes and the other patient (5077IL/0013/0001/0109) had a history of borderline elevated glucose levels. Neither case was considered by the Investigator to be related to treatment with Seroquel.

Apart from the discussed above, none of the other events in Table 5 were considered to be serious by the Investigator, or led to withdrawal from treatment.

5.2.2 Plasma glucose data

5.2.2.1 Mean change from baseline in random plasma glucose levels

The mean changes from baseline to the end of treatment in plasma glucose levels are presented in Table 6 (placebo-controlled trials), Table 7 (short-term comparator-controlled trials) and Table 8 (long-term comparator-controlled trials).

Table 6 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term placebo-controlled trials

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	230	3.60	1.52					
Placebo	143	-0.26	1.93					
Seroquel versus placebo				3.87	2.46	-0.97	8.71	0.1173

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

Table 7 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term comparator-controlled trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	93	-1.30	1.98					
Chlorpromazine	92	-1.20	1.99					
Seroquel versus chlorpromazine				-0.10	2.81	-5.64	5.44	0.9721

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

Table 8 Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	170	4.53	2.57					
Haloperidol	35	4.01	5.68					
Seroquel versus haloperidol				0.52	6.24	-11.79	12/83	0.9333

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

The differences between the treatment groups within each trial pool were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine or Seroquel versus haloperidol).

5.2.2.2 Number of patients meeting criteria for a markedly abnormal plasma glucose level

The number of patients with a plasma glucose level ≥200 mg/dl at any time postbaseline has been summarized in Table 9 (short-term trials) and Table 10 (long-term trials), according to the baseline glucose level.

Table 9 Number (%) of patients with glucose ≥ 200 mg/dl (random values) in short-term trials[a]

Baseline glucose level	Treatment group		
	Seroquel (N=323)	Placebo (N=143)	Chlorpromazine (N=92)
Number of patients with baseline glucose < 200 mg/dl	322	142	92
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	10 (3.1)	1 (0.7)	0
Number of patients with baseline glucose > 200 mg/dl	1	1	0
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	1 (100%)	0 (0)	0
All patients, irrespective of baseline glucose value	**323**	**143**	**92**
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	**11 (3.4)**	**1 (0.7)**	**0**
Total patient year exposure[c]	**28.1**	**10.6**	**8.8**
Incidence density[d]	**0.4**	**0.1**	**0**

[a] From Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006

[b] % uses total number of patients in baseline sub-group as a denominator

[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365

[d] Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dl at any time divided by the total patient year exposure N is based on the number of patients with both baseline and end of treatment glucose data

Table 10 Number (%) of patients with glucose ≥ 200 mg/dl (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	Seroquel (N=170)	Haloperidol (N=35)
Number of patients with baseline glucose < 200 mg/dl	167	32
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	2 (1.2)	1 (3.1)
Number of patients with baseline glucose > 200 mg/dl	3	3
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	3 (100)	2 (66.7)
All patients, irrespective of baseline glucose value	**170**	**35**
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	**5 (2.9)**	**3 (8.6)**
Total patient year exposure[c]	**68.1**	**16.4**
Incidence density[d]	**0.1**	**0.2**

[a] From Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006
[b] % uses total number of patients in baseline subgroup as a denominator

[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dl at any time divided by the total patient year exposure
N is based on the number of patients with both baseline and end of treatment glucose data

The proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the short-term trials was low in all treatment groups (an incidence density of 0.4, 0.1 and 0 in the Seroquel, placebo and chlorpromazine groups, respectively). Similarly, the proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the long-term trials was low in both treatment groups (an incidence density of 0.1 and 0.2 in the Seroquel and haloperidol groups, respectively).

The proportion of patients a postbaseline glucose value ≥ 200 mg/dl did not increase as duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

These data were based on random plasma glucose assessments and are therefore expected to fluctuate depending on the interval since the last meal, glucose content of the last meal, the state of hydration of the patient and many other factors. In order to make a thorough assessment on the effect of Seroquel treatment on plasma glucose levels, narratives of all patients with a glucose value ≥ 200 mg/dl at any time have been prepared and analyzed to assess whether the elevated levels were consistent or sporadic, whether they were extreme, and whether any of the patients concerned had symptoms of diabetes. Full details are provided below.

In total, 20 patients had a plasma glucose level ≥ 200 mg/dl. Of these, 3 patients received haloperidol, 1 patient received placebo and 16 patients received Seroquel. Narratives of all 20 patients are provided in Appendix A.

Three patients who received haloperidol (0012/1205,0021,2105, 0035/3502) had post baseline glucose values >200mg/dl. Two of them had baseline glucose values >200mg/dl and all 3 had histories of hyperglycemia or diabetes.

The single placebo patient with post baseline hyperglycemia had a baseline glucose of 142 mg/dl. Four of 6 post baseline assessments including the final assessment were in excess of 200mg/dl.

A review of the 16 patients who received Seroquel does not suggest a diabetogenic effect of Seroquel, as discussed below:

(a) Patients with a baseline glucose value < 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Twelve of the 16 patients treated with Seroquel had a baseline glucose value < 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl.

In only 5 of the 12 patients was the last glucose value >200mg/dl. In 3 of these 5 patients (0001/0021,0026/2607 and 0034/3411) the baseline value was elevated and slightly less than 200mg/dl (178mg/dl, 192mg/dl and 186mg/dl, respectively). In the remaining 2 patients, repeated hyperglycemia was not observed since only the last glucose determination was ≥200mg/dl.

Seven of the 12 patients had baseline glucose values <200mg/dl, a last glucose of <200mg/dl and at least 1 post baseline assessment of ≥200mg/dl. In 6 of these 7 patients only 1 of several post-baseline assessments was ≥200mg/dl. In the seventh of these patients 3 of 6 determinations were ≥200mg/dl, but the last glucose value was 149.5 mg/dl, only 7.2mg/dl greater than the baseline value.

None of these 12 patients had a blood glucose determination >300mg/dl.

Thus in these 12 patients, sustained hyperglycemia was not observed and the sporadic glucose elevations were not extreme. Further, *none* of the patients had classic symptoms of diabetes, such as polyuria, polydipsia and unexplained weight loss. The glucose values observed are plausibly understood as variations in a parameter that is strongly influenced by the interval since the last meal, glucose content of the last meal, state of hydration and many other factors.

(b) Patients with a baseline glucose value ≥ 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Four of the 16 patients treated with Seroquel had a baseline glucose value ≥ 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl. Two of the 4 patients (0019/1903, 0023/2310) had a history of diabetes. A third had a history of hypothyroidism (0013/1309). The fourth patient's (0020/0005) final blood glucose was lower than baseline.

5.3 Discussion

5.3.1 Adverse event data

The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies (1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials [≤ 6 weeks duration], 4.6% in the long-term controlled [> 6 weeks duration] and 3.6% in the uncontrolled trials).

After adjusting for time-on-study, the incidence of adverse events possibly related to disturbances in glucose metabolism did not increase as the duration of exposure to Seroquel increased (incidence density of 0.6 for the Phase I trials, 0.2 for the short-term controlled trials, 0.2 for the long-term controlled trials and 0.1 for the uncontrolled trials).

A total of 2419 patients was exposed to Seroquel across the Phase I, short- and long-term controlled Phase II/III, and uncontrolled trials in the Seroquel NDA. No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Diabetes mellitus was reported in just 3 (0.1%) patients (5077IL/0012/0046/4603, 5077IL/0014/0036/3605 and 5077IL/0015/0005/0509, Appendix A). All 3 cases were reported in the uncontrolled trials. Two of the 3 patients had a history of diabetes. The third patient is reported to have 'recovered' from the diabetes following treatment with glibenclamide and continued treatment with Seroquel. None of the cases of diabetes mellitus were considered by the Investigator to be related to trial therapy. Further, none of the cases were considered serious by the Investigator or led to withdrawal of treatment.

The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (67 of 2419 patients, 2.8%). Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program had diabetes mellitus (5077IL/0015/0005/0509, Appendix A). This patient had diabetes at baseline (for which they were receiving treatment) and subsequently had 'poorly controlled' diabetes recorded as an adverse event. These observations would indicate that weight gain in patients treated with Seroquel is not a risk factor for the development of diabetes. This is not surprising, as our latest analyses have shown that the actual weight gain associated with Seroquel treatment is minimal, even in the long-term (a mean gain of 1.87 kg [median 1.20 kg] over 1.5 years is observed; for further details see Appendix C). It should be noted that AstraZeneca has already alerted the Prescriber to the possibility of weight gain with Seroquel via the inclusion of a statement in the US Prescribing Information.

There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due events possibly related to glucose dysregulation.

Two patients were withdrawn from treatment due to hyperglycemia (in the uncontrolled trials); both events were considered serious by the Investigator. One of these patients (5077IL/0012/0093/9303, Appendix A) was a known diabetic with a history of hyperglycemia before entering the trial, and the other patient (5077IL/0013/0001/0109, Appendix A) had a history of borderline elevated glucose levels. The investigator did not consider either case to be related to treatment with Seroquel. One patient was withdrawn from treatment due to weight gain (in the short-term controlled trials). Somnolence and abdominal distension were also documented as reasons for withdrawal in this patient. The event was not considered serious by the Investigator.

Apart from the 2 cases of hyperglycemia, none of the other events possibly related to disturbances in glucose regulation in the clinical trial program were considered serious by the Investigator.

5.3.2 Plasma glucose data

The differences between the treatment groups in the mean change from baseline in plasma glucose data in short-term trials and long-term trials were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine [short-term trial] or Seroquel versus haloperidol[long-term trial]).

The proportion of patients with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

A detailed review of the patients with a glucose value ≥ 200 mg/dl revealed that the majority of elevations were sporadic (ie not consistently observed during treatment) and did not exceed 300 mg/dl at any time. Further, *none* of the patients had symptoms of diabetes. It is likely that the values observed reflect variations in a parameter that is strongly influenced by the interval since that last meal, glucose content of the last meal, state of hydration, and many other factors.

5.4 Conclusion

In conclusion, a thorough review of all the adverse event data and plasma glucose data in the clinical trial program has revealed no clear evidence of a causal association between Seroquel treatment and disturbances in glucose regulation. In addition, there was no evidence from the clinical data of a direct link between weight gain in patients treated with Seroquel and the onset of diabetes.

6 REVIEW OF POSTMARKETING DATA

In response to Part 3 of the FDA's request, spontaneous postmarketing reports received by AstraZeneca since Seroquel's US approval (September 1997) up to May 2000 have been thoroughly reviewed for possible cases of hyperosmolar coma, new-onset diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain.

6.1 Results

6.1.1 Hyperosmolar coma

There have been no postmarketing reports of hyperosmolar coma.

6.1.2 New-onset diabetes mellitus

There have been 12 spontaneous postmarketing reports of new-onset diabetes mellitus (including 2 literature reports). Narratives of all 12 patients are presented in Appendix B.

The age range for patients with new onset diabetes mellitus is 12 to 48 years, with an average age at onset of 32.5 years (median = 34 years). There is a male predominance, with males constituting 75% of all reports. Daily Seroquel dosages ranged from 50 mg to 750 mg, with an average daily dose of 385 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 4.9 months with a range of 15 days to 21 months (median = 2.0 months). Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl (median 474= mg/dl).

Weight gain was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 1999UW03532).

Weight loss was reported in 1 of the 12 patients with new-onset diabetes (2000UW01164).

Diabetic ketoacidosis was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 2000UW01164).

Dose-related loss of glycemic control was reported in 2 of the 12 patients with new-onset diabetes mellitus (1999UW00969 and 1998UW48512).

One patient developed Type 1 diabetes mellitus (2000UW00266).

In addition to the 12 patients with new-onset diabetes described above, AstraZeneca has received 4 reports describing exacerbation of pre-existing diabetes mellitus.

6.1.3 Diabetic ketoacidosis

There have been 3 postmarketing spontaneous reports of diabetic ketoacidosis. Narratives of all 3 patients are presented in Appendix B.

The age range is 25 to 58 with an average age at onset of 42 years (median= 43 years). All 3 patients were male. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 583 mg (median = 750 mg). The average time interval between initial therapy and the date of the reported event was 11.0 months with a range of 1 to 21 months (median =11 months). Blood glucose concentrations at clinical presentation for these patients were not provided.

Two of the 3 patients with diabetic ketoacidosis also developed new-onset diabetes mellitus. (1999AP05757 and 2000UW01164). The former patient gained an unspecified amount of weight and the latter patient lost 13.6 kg.

Another patient (1998UW49554) with a pre-existing diabetic condition died due to complications of diabetes mellitus.

6.1.4 Hyperglycemia

There have been 2 postmarketing spontaneous reports of hyperglycemia. Narratives of both patients are presented in Appendix B.

Blood glucose concentrations were not provided for either patient. One report (2000UW01047) involved a 47-year-old female who developed weight gain and hyperglycemia after taking Seroquel 150 mg daily for 30 months. The other report (1998AP50408) contains scant information, except the daily Seroquel dose which was 750 mg.

6.1.5 Weight gain

There have been 38 spontaneous postmarketing reports and 4 literature reports of weight gain associated with Seroquel therapy.

Patients ranged in age from 8 to 70 years of age with a mean of 38 years (median = 36 years). There is a slight female predominance with females constituting 55% of reports in which gender was specified. Reported weight gain ranged from 0.9 kg to 31.8 kg with the average reported weight gain being 12.5 kg (median = 10.7 kg). The average time interval between initial therapy and the date of the reported event was 6.8 months with a range of 10 days (2.2 kg) to 2 years (18.1 kg) and a median of 4 months.

Diabetes mellitus was reported in 2 of the 38 patients with weight gain (1999AP05757 and 1999UW03532).

6.2 Discussion

Since the approval of Seroquel in the US in September 1997, it is estimated that over 623,000 patients have been exposed to Seroquel (see Section 7). Despite this extensive exposure, only a small number of cases of diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain have been reported.

Many of the cases reported had confounding factors. Six of the 12 patients with new-onset diabetes were reported as using concomitant medications known to be associated with glucose dysregulation and diabetes mellitus, including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, and 1999UW00969). Few, if any, of the 12 patients had baseline fasting glucose levels.

One of the 3 patients with diabetic ketoacidosis (2000UW01164) is reported to have used concomitant medications known to impair glucose tolerance and cause diabetes mellitus (venlafaxine). Another patient (1998UW49554) had a pre-existing diabetic condition.

In the patients with weight gain, there are several confounding factors to note. Two patients (1999UW01496 and 1998UW46392) developed edema and 1 patient (1999AP00761) was diagnosed with congestive heart failure. Edema and heart failure are both labeled adverse events that are known to contribute to weight gain secondary to fluid retention and accumulation. There was 1 report (1999UW02120) describing a negative dechallenge in which the accrued weight remained despite discontinuation of Seroquel treatment. Two patients (1999UW02120 and 1998UW48690) had concomitant hypothyroidism, a known cause for weight gain. In addition, 1 patient (1999AP05242) developed hypothyroidism after starting Seroquel treatment.

Unfortunately, several postmarketing reports contained only scant information that precluded further detailed analysis of these cases.

The current US Seroquel package insert is labeled for diabetes mellitus, hyperglycemia, and weight gain as Adverse Reactions. Details are provided below.

Under the category of Other Adverse Events Observed During the Pre-marketing Evaluation of SEROQUEL in the insert, diabetes and hyperglycemia are listed as an infrequent experience (events occurring in 1/100 to 1/1000 patients). Weight gain (2%) is included as a treatment-emergent adverse experience in 3- to 6-week placebo-controlled clinical trials. The package insert also alerts the Prescriber to a statistically significantly greater incidence of weight gain (≥ 7% of body weight) for SEROQUEL (23%) compared to placebo (8%). In addition, reference is made

to spontaneously elicited adverse event data from a study comparing five fixed doses of Seroquel (75 mg, 150 mg, 300 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. The insert states that logistic regression analysis revealed a positive dose response ($p < 0.05$) for weight gain in this analysis.

The package insert does not contain any details of diabetic ketoacidosis or hyperosmolar coma. However, only 3 spontaneous reports of diabetic ketoacidosis have been received to date in patients using Seroquel (indicating that there does not appear to be a signal that Seroquel is associated with diabetic ketoacidosis) and there have been no reported cases of hyperosmolar coma.

AstraZeneca has paid particular attention to the incidence of patients with both weight gain and diabetes. Only 2 patients were reported to have had concomitant weight gain and diabetes mellitus. Thus there does not appear to be a link between these 2 conditions.

6.3 Conclusion

It is concluded that that the current Seroquel package label accurately describes patient experiences to date of diabetes mellitus (and related complications), hyperglycemia, and weight gain.

7 PATIENT EXPOSURE ESTIMATION

In response to Part 4 of the FDA's request, AstraZeneca has calculated the extent of exposure to Seroquel across the clinical trial program, and estimated the extent of exposure to Seroquel from postmarketing experience.

7.1 Clinical trials

7.1.1 Phase I trials

A total of 300 patients were exposed to Seroquel in the Phase I trials.

The mean daily dose and duration of Seroquel use in the Phase I clinical trials are presented in Table 11.

Table 11 Mean daily dose and duration of exposure to Seroquel in the Phase I trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	33	0	0	0	0	0	33 (11)
2 to 7	83	5	10	1	0	0	99 (33)
8 to 14	1	3	19	18	29	0	70 (23)
15-21	0	0	21	46	9	7	83 (28)
22-35	0	8	1	5	1	0	15 (5)
Total (%)	117 (39)	16 (5)	51 (17)	70 (23)	39 (13)	7 (2)	300 (100)

Approximately 40% of subjects received Seroquel for less than 7 days. A total of 55% of subjects had mean doses of Seroquel within the clinically effective dose range (>150 to < 800 mg/day). Fifteen percent of subjects had mean daily doses that were greater than 450 mg/day.

7.1.2 Controlled Phase II/III trials

A total of 1710 patients were exposed to Seroquel in the controlled Phase II/III trials.

The mean daily dose and duration of Seroquel use in the controlled Phase II/III clinical trials are presented in Table 12.

Table 12 Mean daily dose and duration of exposure to Seroquel in the controlled Phase II/III trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	14	0	0	0	1	0	15 (1)
2 to 7	59	24	60	4	1	0	148 (9)
8 to 14	63	17	60	79	21	2	242 (14)
15 to 21	36	22	37	55	19	2	171 (10)
22 to 28	23	6	23	40	19	1	112 (7)
29 to 35	17	2	16	24	9	8	76 (4)
36 to 42	97	26	94	285	138	63	703 (41)
43 to 112	39	6	29	51	27	9	161 (9)
113 to 183	5	0	7	0	9	0	21 (1)
184 to 365	16	4	15	0	20	0	55 (3)
366 to 548	0	0	2	0	3	1	6 (0)
Total (%)	369 (22)	107 (6)	343 (20)	538 (32)	267 (16)	86 (5)	1710 (100)

Most subjects (86%) received Seroquel for 6 weeks or less because most exposure in the controlled trials occurred in short-term trials. The majority of subjects (72%) had mean daily doses of Seroquel that were greater than 150 mg/day; 21% had mean daily doses that were greater than 450 mg/day.

7.1.3 Uncontrolled Phase II/III trials

A total of 1256 patients were exposed to Seroquel in the uncontrolled trials. Of these, 847 patients had taken part in the controlled trial program.

The mean daily dose and duration of Seroquel use in the uncontrolled Phase I/III clinical trials are presented in Table 13.

Table 13 Mean daily dose and duration of exposure to Seroquel in the uncontrolled trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	6	1	1	0	0	0	8(1)
2 to 7	17	18	31	11	2	1	80(6)
8 to 14	7	4	27	19	22	7	86 (7)
15 to 21	7	2	10	30	25	15	89 (7)
22 to 28	8	5	25	40	28	18	124 (10)
29 to 35	2	2	5	15	29	13	66 (5)
36 to 42	3	6	10	10	14	14	57 (5)
43 to 112	10	12	36	57	80	82	277 (22)
113 to 183	1	2	24	49	65	46	187 (15)
184 to 365	1	5	41	58	60	62	227 (18)
366 to 548	0	1	8	10	16	17	52 (4)
549 to 730	0	0	1	0	0	1	2 (0)
730	0	0	0	0	0	1	1 (0)
Total (%)	62 (5)	58 (5)	219 (17)	299 (24)	341 (27)	277 (22)	1256 (100)

A total of 59% of subjects had been given Seroquel for longer than 6 weeks: 282 subjects were exposed to Seroquel for 6 months or longer, 55 subjects were exposed for more than 1 year and 1 subject was exposed to Seroquel for more than 2 years. Most subjects (90%) had mean daily doses of Seroquel that were greater than 150 mg/day, whereas 49% of subjects had mean daily doses greater than 450 mg/day.

7.2 Postmarketing experience

It is difficult to obtain a precise estimate of the number of patients that have been exposed to Seroquel since launch. However, a recent audit of the NDC database indicated that, on average, a patient received 3.84 prescriptions for Seroquel. In post-launch period to 30 June 2000, 2,393,000 prescriptions have been written for Seroquel in the US. This would suggest that approximately 623,000 unique patients have been exposed to Seroquel since launch, representing approximately 199,000 patient years (assuming that each prescription covers a 1- month period).

8 CORRESPONDENCE WITH REGULATORY AGENCIES

In response to Part 5 of the FDA's request, AstraZeneca has reviewed all correspondence with regulatory agencies regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

8.1 Results

There have been no issues raised verbally or formally in correspondence with foreign regulatory agencies related to the events of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, and hyperglycemia associated with Seroquel.

Questions relating to weight gain during the clinical program were asked by the French and Swiss agencies during their national reviews and also by Spain during the question and answer period in the European Mutual Recognition (MR) procedure conducted in the latter half of 1999.

In preclinical assessment, the Swedish Medical Products Agency (MPA) and the Japanese Ministry of Health and Welfare (MHW) asked the same question during their national reviews regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study. This topic is also addressed in Part 1 of this FDA response.

Copies of all the questions and company responses are provided in Appendix D.

8.2 Discussion

In terms of weight gain, it should be noted that the company has already taken the step globally of alerting the Prescriber to the possibility of limited weight gain with Seroquel via the inclusion of a statement in Section 4.9 (possible adverse reactions) of the Core Data Sheet for the product.

In the spirit of this, the Adverse Reactions section of the US Professional Information Brochure advises the physician that there is a statistically significantly greater incidence of weight gain for Seroquel (23%) compared to placebo (6%).

The explanation given to both MPA and MHW regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study was accepted by both agencies.

9 POTENTIAL COLLABORATION WITH OTHER DATABASES

We are investigating the possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

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APPENDIX A

Patient narratives: clinical data

Patients withdrawn from treatment due to adverse events possibly associated with disturbances in glucose metabolism

5077IL/0012/ 0007/0708 Seroquel

Abdomen enlarged, Weight gain, Somnolence

This 37-year old, white woman with chronic paranoid schizophrenia was withdrawn on Day 10 for abdominal distension, abnormal weight gain, and drowsiness while receiving Seroquel 450 mg/day, administered on a twice-daily basis. The drowsiness resolved 1 day later. Her weight gain was 2.0 kg over 2 weeks, and returned to pretrial levels 6 days after withdrawal, as did the abdominal distension. She was receiving no concurrent medication at entry and had an unremarkable medical history other than tubal ligation. The abdominal distension, abnormal weight gain, and drowsiness were considered by the investigator to be probably related to Seroquel.

5077IL/0012/ 0093/9304 Seroquel

Hyperglycemia

This 53-year-old, white woman with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 34 (Seroquel 200 mg/day) due to hyperglycemia (glucose value not available). The subject was a known diabetic and had hyperglycemia noted prior to entry into the trial. Other significant medical history included hypertonia and angina. Concurrent medications included ascorbic acid/ferrous sulfate combination, insulin protamine injection/insulin regular combination, glycerol trinitrate, fenofibrate, REDACTED, insulin protamine injection, insulin regular, and drotaverine. On Day 18 (Seroquel 200 mg/day), hyperglycemia (COSTART term hyperglycemia) was reported as an adverse event (glucose value not available). The hyperglycemia resolved 3 weeks (Day 55) after withdrawal from trial treatment. The event was considered by the investigator to be moderate in intensity and probably not related to trial treatment.

5077IL/0013/ 0001/0109 Seroquel

Hyperglycemia

This 44-year-old, black man with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 10 (Seroquel 150 mg/day) due to hyperglycemia. Medical history was significant for borderline elevated glucose levels (untreated), Bell's palsy, back pain, gynecomastia, peptic ulcer disease, hiatal hernia, obesity, abdominal discomfort, and urinary hesitancy. Concurrent medications included ranitidine, pseudophedrine/triprolidine combination, and glipizide. On Day 8, the fasting blood glucose level previously drawn was discovered to be 392.72 mg/dl (normal range 68 to 115 mg/dl). A repeat level drawn on Day 8 was 407.1 mg/dl. The subject was sent to the emergency room for a medical consult, where he was started on glipizide and placed on a special diet prior to his return to the unit that same day. On Day 10 (Seroquel 600 mg), he complained of nausea, dizziness, and blurred vision, and vomited his lunch. A blood glucose level was immediately drawn with a result of 1104.3 mg/dl. The subject was again transferred to the emergency room and was admitted to the medical intensive care unit of the hospital, where he was started on intravenous insulin and hydration. At this time, trial treatment was discontinued. By Day 11, his blood glucose had decreased to the 198.1 mg/dl range and the subject had otherwise returned to his baseline health. The insulin drip was discontinued on Day 12 and he was maintained on subcutaneous insulin until Day 15, when this was switched to glyburide and he was transferred back to his original unit. Glucose remained stable in the 198.1 mg/dl range. The subject did not receive any further trial treatment after Day 10 due to difficulties in following the subject at another hospital. The investigator considered restarting the subject on the trial treatment once he returned to his original unit; however, at the request of the subject's spouse, this was not done. The investigator considered the hyperglycemia to be severe in intensity and not related to trial treatment.

Patients with adverse events of diabetes mellitus

5077IL/0012/0046/4603 Seroquel (controlled trials), Seroquel (open label extension)

This patient is a 35-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day. The patient had a history of eye esotropia and diabetes mellitus. The patient was receiving daonil for diabetes before the start of the trial. During the trial adverse events of weakness, sleepiness and constipation were all reported as mild and possibly related. The patient discontinued Seroquel therapy at a dose of 450 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of headache, insomnia and unstable diabetes were reported. The unstable diabetes was reported 9 days into open label treatment. The patient was receiving 300 mg/day Seroquel. The event was considered 'moderate' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed insulin and glucophage for the diabetes.

5077Il/0014/0036/3605 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 51-year old white female presenting with paranoid schizophrenia who began haloperidol at a dose of 1mg/day. The patient had a past history of hypertension.

During the trial the adverse event of moderate hypertension, related to therapy, was recorded. The patient discontinued haloperidol therapy at a dose of 10 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of diabetes mellitus and infection were reported. The diabetes mellitus was reported 61 days into open label treatment. The patient was receiving 400 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide for the diabetes.

5077IL/0015/0005/0509 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 40-year old black female presenting with paranoid schizophrenia who began haloperidol at a dose of 2 mg/day. She had a medical history of otitis media, tooth infections, chronic headaches, EPS (benzatropine), cardiomegally (mild hypertension), bronchitis, urinary tract infection (salpingeltomy), diabetes, depression (nortriptyline), anxiety (lorazepam), insomnia (chloral hydrate). The patient was prescribed glibenclamide for the diabetes before the trial.

During the trial adverse events of hand tremors, muscle stiffness and cogwheel rigidity were all reported as moderate and probably related were reported. The patient discontinued haloperidol therapy at a dose of 12 mg/day on Day 28. The reason for discontinuation was reported as adverse reaction/intercurrent illness.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of tongue tremors, constipation, weight gain, tooth abscess, septicemia, insomnia and poorly controlled diabetes mellitus were reported. The diabetes mellitus was reported 344 days into open label treatment. The patient was receiving 500 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide and received insulin injections for the diabetes.

Patients with plasma glucose ≥ 200 mg/dl at any time

204636/0007/0003/0002 Seroquel

This patient is a 35-year old white female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 50mg/day on 16-May-1991(Day 0). She had a medical history of anemia (ferrous sulfate, folic acid), psychosis (lithium carbonate, stelazine) and depression (lofepramine). Pre-trial antipsychotic medication was not recorded. She received EPS medications -unspecified (agitation), benzodiazepines (agitation) and chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 1000mg/day by Day 19. The patient's weight was 63.0kg on Day 0 and 66.0kg on Day 27.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
15-May-91 (1)	162
23-May-91 (7)	133.3
30-May-91 (14)	221.6
05-Jun-91 (20)	97.3
12-Jun-91 (27)	86.5

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'treatment failure'.

204636/0008/0001/0021 Seroquel

This patient is a 21-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 05-Aug-1991(Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 76.2kg on Day 0 and 76.2kg on Day 10.

During treatment adverse events of drowsiness, depressed thyroid stimulation, thyroxine and triiodothyronine were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
26-July-91 (-10)	178.3
12-Aug-91 (7)	207.2

The patient discontinued Seroquel therapy at a dose of 50 mg/day on Day 10. The reason for discontinuation was reported as 'refused to continue'.

204636/0008/0005/0003 Seroquel

This patient is a 55-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-Sept-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 6. The patient's weight was 81.0kg on Day 0 and 82.0kg on Day 41.

During treatment an adverse event of severe agitation which was possibly related was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
29-Aug-91 (-4)	167.5
17-Sept-91 (15)	210.8
23-Sept-91 (21)	196.4
01-Oct-91 (29)	129.7
09-Oct-91 (37)	106.3
14-Oct-91 (42)	90.1

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0009/0002 Seroquel

This patient is a 59-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day on 20-Aug-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded.

During the trial the patient was dosed Seroquel up to a level of 350mg/day by Day 13. The patient's weight was 88.9kg on Day 0 and 91.6kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Aug-91 (-6)	142.3
27-Aug-91 (7)	230.6
02-Sept-91 (13)	221.6
09-Sept-91 (20)	129.7
16-Sept-91 (27)	252.2
23-Sept-91 (34)	136.9
30-Sept-91 (41)	149.5

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0020/0005 Seroquel

This patient is a 44-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 25-July-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 5. The patient's weight was 75.2kg on Day 0 and 77.5kg on Day 27.

During treatment adverse events of probably related moderate headache and possibly related moderate agitation were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
24-July-92 (-1)	234.2
31-July-92 (6)	257.6

07-Aug-92 (13)	322.5
13-Aug-92 (19)	264.8
20-Aug-92 (26)	226.9
24-Aug-92 (30)	-

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'refused to continue'

204636/0008/0026/0001 Seroquel

This patient is a 38-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 13-May-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 500mg/day by Day 9. The patient's weight was 79.0kg on Day 0 and 78.0kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
30-Apr-92 (-13)	118.9
20-May-92 (7)	100.9
09-Jun-92 (27)	198.2
16-Jun-92 (34)	205.3
23-Jun-92 (41)	172.9

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0026/0006 Placebo

This patient is a 41-year old white female presenting with paranoid schizophrenia who began the trial on 14-July-1992 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel placebo. The patient's weight was 110.0kg on Day 0 and 115.0kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Jul-92 (0)	142.3
21-Jul-92 (7)	167.5
28-Jul-92 (14)	223.4
04-Aug-92 (21)	120.7
11-Aug-92 (28)	207.2
18-Aug-92 (35)	219.8
25-Aug-92 (42)	223.4

The patient discontinued on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0028/0110 Seroquel

This patient is a 36-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 08-Nov-1991 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 75.5kg on Day 0 and 74.6kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Nov-91 (-4)	160
14-Nov-91 (6)	154
22-Nov-91 (14)	137
29-Nov-91 (21)	131
06-Dec-91 (28)	218

13-Dec-91 (35)	158
20-Dec-91 (42)	148

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0031/0403 Seroquel

This patient is a 36-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 10-Mar-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received chloral hydrate (sleep) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 11. The patient's weight was 76.8kg on Day 0 and 77.3kg on Day 22.

During treatment an adverse event of possibly related mild dizziness was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
06-Mar-92 (-4)	103
17-Mar-92 (7)	155
24-Mar-92 (14)	190
01-Apr-92 (22)	228

The patient discontinued Seroquel therapy at a dose of 550mg/day on Day 22. The reason for discontinuation was reported as 'lack of efficacy'.

5077IL/0004/0001/0008 Seroquel

This patient is a 40-year old black male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 09-Jan-1990 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 200mg/day by Day 12. The patient's weight was 83.6kg on Day 0 and 90.9kg on Day 20.

During treatment adverse events of elevated SGPT, sedation, headache and tachycardia were reported, these were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Jan-90 (-5)	74
09-Jan-90 (0)	106.3
13-Jan-90 (4)	259.4
17-Jan-90 (8)	122.5
21-Jan-90 (12)	104.5
25-Jan-90 (16)	113.5
29-Jan-90 (20)	111.7

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 20. The reason for discontinuation was reported as 'completed study'.

5077IL/0006/0001/0114 Seroquel

This patient is a 58-year old black male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 07-Jan-1992 (Day 0). He had a pre-trial medical history of eczema, fungal infection, hypertension, hepatomegaly, scrotal mass, perianal fissures, dementia, cataracts, schizophrenia, bipolar disorder and tardive dyskinesia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 27. The patient's weight was 61.4kg on Day 0 and 61.4kg on Day 34 and his height was recorded as 175 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
03-Jan-92 (-4)	97
13-Jan-92 (6)	95
20-Jan-92 (13)	115

27-Jan-92 (20)	73
03-Feb-92 (27)	62
10-Feb-92 (34)	215

The patient discontinued Seroquel therapy at a dose of 750mg/day on Day 34. The reason for discontinuation was not recorded.

5077IL/0006/0011/1110 Seroquel

This patient is a 48-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 19-Mar-1992 (Day 0). He had a pre-trial medical history of tardive dyskinesia and schizophrenia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation, insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 600mg/day by Day 29. The patient's weight was 82.5kg on Day 0 and 86.8kg on Day 41 and his height was recorded as 173 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Mar-92 (-2)	133
25-Mar-92 (6)	157
01-Apr-92 (13)	186
08-Apr-92 (20)	193
15-Apr-92 (27)	210
22-Apr-92 (34)	164
29-Apr-92 (41)	158

The patient discontinued Seroquel therapy at a dose of 400mg/day on Day 41. The reason for discontinuation was reported as 'completed study'

5077IL/0015/0012/1205 Haloperidol

This patient is a 34-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 18-Feb-1994 (Day 0). He had a pre-trial medical history of bronchitis, hyperglycemia, and alcohol and drug abuse. Pre-trial the patient received haloperidol for schizophrenia, this was stopped on 17-Feb-1994 (Day -1). He received the following concomitant medication during the trial: cogentin (EPS prophylaxsis), diabeta (hyperglycemia), hydrocodone, iodine, aspirin (left foot pain, body aches), prozac (unknown), contac (nasal congestion), 4-way nasal spray (nasal congestion), sinutab (sinus headaches), orudis (groin pain), flexeril, voltaren (left sciatic pain) and erythromycin (sore throat). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 6. The patient's weight was 136.4kg on Day 0 and 130.5kg on Day 357 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the study were as follows:

Date (day)	Glucose mg/dl
17-Feb-94 (-1)	268
04-Aug-94 (167)	516
16-Feb-95 (357)	328

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0013/1309 Seroquel

This patient is a 43-year old hispanic female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 18-May-1994 (Day 0). She had a pre-trial medical history of head injury, anemia, hepatitis, hypothyroidism, substance abuse and pollen allergies. Pre-trial the patient received trifluoperazine for schizophrenia, this was stopped on 17-May-1994 (Day -1). She received the following concomitant medication during the trial: propanolol (akathisia , anxiety), cogentin (EPS), triphosil-28 (oral contraceptive), chloral hydrate (anxiety), lorazepam (agitation), chlortrimetan (sinus congestion), flu shot (flu prevention), ibuprofen and tylenol (intermittent back/neck pain) During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 106.4kg on Day 0 and 99.1kg on Day 358 and her height was recorded as 168 cm.

During treatment an adverse event of increased sedation was reported, this was reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-May-94 (-9)	254
31-Oct-94 (166)	250
14-May-95 (358)	122

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 358. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0019/1903 Seroquel

This patient is a 46-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 23-Nov-1993 (Day 0). She had a pre-trial medical history of headaches, non insulin dependent diabetes and obesity. Pre-trial the patient received tiotixene for schizophrenia, this was stopped on 22-Nov-1993 (Day -1). She received the following concomitant medication during the trial: diabeta (non insulin dependent diabetes), lorazepam (agitation), lorcet plus, tylenol (headaches), tavist-D (nasal congestion), cataflam, oruvail and flexeril (back pain). The patient was dosed Seroquel at a level of 75mg/day throughout the trial. The patient's weight was 109.5kg on Day 0 and 109.5kg on Day 357 and her height was recorded as 168 cm.

During treatment adverse events of intermittent insomnia and constipation were reported, these were reported as mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-Nov-93 (-12)	245
10-May-94 (168)	313
15-Nov-94 (357)	434

The patient discontinued Seroquel therapy at a dose of 75mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0021/2105 Haloperidol

This patient is a 63 year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 21-Dec-1993 (Day 0). He had a pre-trial medical history of

rash, hypertension, benign prostatic hypertrophy, shortness of breath and untreated elevated blood sugar. Pre-trial the patient received perphenazine for psychosis, this was stopped on 20-Dec-1993 (Day -1). He received the following concomitant medication during the trial: benadryl, chloral hydrate (insomnia) and lorazepam (agitation). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 9. The patient's weight was 109.1kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment an adverse event of probably related mild sedation was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
13-Dec-93 (-8)	327
03-Jan-94 (13)	282

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 15. The reason for discontinuation was reported as 'refused to continue'

5077IL/0015/0023/2310 Seroquel

This patient is a 43-year old male of 'other' ethnic origin presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-July-1994 (Day 0). He had a pre-trial medical history of sinus bradycardia, mild peptic ulcer and stable insulin dependent diabetes. Pre-trial the patient received chlorpromazine for psychosis, this was stopped on 24-Jun-1994 (Day -8). He received insulin NPH (diabetes) during the trial. During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 58.6kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Jun-94 (-15)	363
30-Aug-94 (59)	406

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 59. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0026/2607 Seroquel

This patient is a 52-year old asian male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 15-Dec-1993 (Day 0). He had a pre-trial medical history of myocardial infarction and increased cholesterol. Pre-trial the patient received perphenazine for psychosis, this was stopped on 14-Dec-1993 (Day -1). He received the following concomitant medication during the trial: lorazepam (agitation), lithobid (adjunct Tx schizophrenia), temazepam, chloral hydrate (insomnia), aspirin (heart condition) and mevacor (hypercholesterolemia). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 8. The patient's weight was 79.5kg on Day 0 and 79.3kg on Day 12 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Dec-93 (-1)	192
28-Dec-93 (13)	240

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 12. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0034/3411 Seroquel

This patient is a 41-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 14-Oct-1994 (Day 0). She had a pre-trial medical history of tubal ligation, substance abuse and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Oct-1994 (Day -1). She received the following concomitant medication during the trial: benzatropine (EPS prophylaxsis), desipramine (depression) and micronase (diabetes). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 6. The patient's weight was 101.4kg on Day 0 and 122.7kg on Day 209 and her height was recorded as 168 cm.

During treatment an adverse event of mild dizziness was reported, this was mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl

05-Oct-94 (-9)	186
21-Apr-95 (168)	259

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 209. The reason for discontinuation was reported as 'completed study'.

5077IL/0015/0035/3502 Haloperidol

This patient is a 43-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 14-Mar-1994 (Day 0). He had a pre-trial medical history of depressed hypertension, elevated liver enzymes and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Mar-1994 (Day -1) . He received the following concomitant medication during the trial: lorazepam (agitation), lithium, nortriptyline (depression), glucotrol (diabetes), accupril (hypertension), ativan (increased anxiety), vantin (URI), tylenol, motrin (headache), chloral hydrate (insomnia), alcaine, cyclogyl, mydfrin, profenal, BSS, dexamethasone, garamycin and viscoat (cataract surgery). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 5. The patient's weight was 108.2kg on Day 0 and 106.8kg on Day 364 and his height was recorded as 168 cm.

During treatment an adverse event of serious cataract surgery, unrelated to trial therapy, was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
08-Mar-94 (-6)	191
30-Aug-94 (169)	364
13-Mar-95 (364)	209

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 364. The reason for discontinuation was reported as 'completed protocol'.

APPENDIX B

Patient narratives: postmarketing data

Cases of new-onset diabetes mellitus

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose levels

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 13.6 kg. Fasting blood sugar showed glucose level over 700 mg/dl. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

2000UW00266 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 12-year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170 mg/dl. Concomitant medications include Zoloft, Klonopin, Haldol and depakote.

Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

1999UW03532 Seroquel

Diabetes mellitus, weight gain

A report has been received from a physician concerning a 45-year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes.

Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

1999UW03387 Seroquel

Type II diabetes, drowsiness

A report has been received from a physician concerning a 17-year old Hispanic male patient who had been receiving Seroquel 100 mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

1999UW00969 Seroquel

Complications of diabetes mellitus

A report has been received from a physician concerning a 28-year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240 mg/dl, potassium low, CPK normal, lithium level was not elevated (0.4 or 0.6 mEq/L). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on REDACTED The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending. Follow-up has been requested.

*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no dolls eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli.

Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on REDACTED The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 4.5 to 7.3 kg weight loss with flu-like symptoms, and blood glucose of 123.8 mg/dl on admission.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 months after starting Seroquel fumarate, the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

1999AP05218 Seroquel

Diabetes during pregnancy

No further information available.

1999AP02989 Seroquel

Diabetes mellitus

This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 308 mg/dl.

1998UW48512 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 98, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycemia. Four months prior to admission blood glucose was 126 mg/dl and 107 mg/dl. At admission blood glucose was 607 mg/dl. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

This patient's details have been published in a literature case report (Sobel, Jaggers and Franz, 1999).

1999AP01985 Seroquel

Non-insulin dependent diabetes

Terse Narrative: Concomitant medication includes cyproterone acetate which can influence carbohydrate metabolism.

1998UW48844 Seroquel

Hyperglycemia, diabetes

A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for 4 weeks and is experiencing hyperglycemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl. Follow-up will be requested.

1999UW00967 Seroquel

Diabetes

A report has been received from a physician concerning a 17-year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Cases of diabetic ketoacidosis

1998UW49554 Seroquel

Cerebrovascular accident, diabetic acidosis, transient ischemic attack, collapse

A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose level

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 months after starting Seroquel, the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced

weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

Cases of hyperglycemia

2000UW01047 Seroquel

Cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, excitable, difficulty in waking, negative mood, decreased sex drive, inability to have orgasms

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

1998AP50408 Seroquel

Hyperglycemia (non-serious)

Pharmacist considers hyperglycemia unrelated to Seroquel, however patient's nurse considers the event related.

APPENDIX C

The effect of Seroquel on weight gain

Source material

The weight information provided below has been taken from the interim assessment of Seroquel Trial 5077IL/0051 (an open label extension [OLE] trial; data cut-off date March 28 2000).

Trial 5077IL/0051 is an international, multicentre, open-label extension of treatment with Seroquel for schizophrenic patients who have participated in the Seroquel Phase IIIb clinical trial program (namely Trials 0050, 0052, 0053 and 0054).

Open treatment with Seroquel began, in most cases, with an initial dose-titration period during which the dose was increased according to the patient's clinical condition. Thereafter, Seroquel dosing was flexible, up to a maximum of 800 mg/day, administered twice daily.

Weight data for the analyses are taken from patients who were exposed to Seroquel either during randomized treatment in the feeder trial or open-label Seroquel treatment during OLE.

Analyses

To observe the effect of Seroquel monotherapy on weight gain, the following analyses were undertaken:

- **The effect of Seroquel monotherapy on weight over time (between 1 and 1.5 years)**
  - in patients with weight data *both* at baseline and at 1 specific timepoint during treatment with Seroquel monotherapy: Weeks 53-78

  If a patient had more than 1 visit within each timepoint, then the mean value was taken.

- **The effect of Seroquel monotherapy on weight across the dose range**
  - in patients with weight data at baseline and endpoint

  Data were classified into the following 3 dose ranges (according to the patient's dose of Seroquel at endpoint): ≤ 300 mg, > 300 mg to ≤ 500 mg, > 500 mg. (It should be noted that time on treatment for each patient in this cohort will vary).

Results

In patients with weight data both at baseline and at 1 specific timepoint during Seroquel monotherapy treatment (between 1 and 1.5 years), the mean weight change was 1.87 kg and the median weight change was 1.20 kg (Tables C1 and C2).

Weight change observed at the end of treatment with Seroquel monotherapy was consistent across the dose range (Tables C3 and C4).

Table C1 Patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel	
	Weeks 1-4 (n=130)	Weeks 53-78 (n=130)
Mean weight (kg)	72.57	74.44
Median weight (kg)	70.25	72.00
SD	15.50	15.59
Min	43.0	45.6
Max	128.7	136.0

Table C2 Change from first dose of Seroquel in patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel
	Weeks 53-78 (n=130)
Mean weight change (kg)	1.87
Median weight change (kg)	1.20
SD	7.63
Min	-27.2
Max	25.5

Table C3 Patient absolute weight at baseline and endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Baseline				
Mean weight (kg)	75.88	73.91	73.10	74.37
Median weight (kg)	73.40	71.75	69.70	71.50
SD	16.13	17.08	15.10	14.83
Min	47.5	43.0	50.2	46.2
Max	128.0	146.0	130.0	126.0
Endpoint				
Mean weight (kg)	77.10	74.66	73.30	74.04
Median weight (kg)	75.00	72.00	72.50	72.00
SD	15.69	19.30	16.52	15.52
Min	45.0	46.0	45.8	43.9
Max	128.5	172.8	140.0	135.0

Table C4 Change in weight from baseline to endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Mean weight change (kg)	1.21	0.75	0.20	-0.34
Median weight change (kg)	1.00	-0.25	-0.60	0.00
SD	7.33	7.25	7.86	7.91
Min	-21.8	-14.5	-21.4	-27.2
Max	26.5	26.8	27.3	23.0
N	103	72	71	134

Summary

The effect of Seroquel on weight change in the long-term is minimal. There does not appear to be any relationship between weight change and the dose of Seroquel.

APPENDIX D

Correspondence with regulatory agencies

APPLICATION FOR MARKETING AUTHORIZATION
-MR PROCEDURE

Seroquel (REF No NL/H/156/01-03)
Quetiapine Zeneca (Ref No NL/H/157/01-03)

Consolidates Response to Concerned Member States

November 1999

COUNTRY : SPAIN SPC Question number ES-7:

According to SPC, quetiapine was associated with weight gain predominantly during the early weeks of treatment but the results of controlled and uncontrolled trials showed a duration-related increase in the incidence of clinically significant weight increase. This issue should be clarified.

AstraZencea response:

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

The apparent inconsistency identified by the reviewer is driven by 2 distinct factors. Firstly, the 2 columns in Table 59 in the Clinical Data Summary (number [%] with >7% the baseline weight and total mean weight increase [kg], respectively) are not directly comparable. The total mean weight increases have been calculated using the *last value* for each patient within each time period. (These mean weight change also takes into account patients who lose weight). The other column, however, reports all patients who exceeded the 7% threshold *at any time* during the time period, including transient effects.

In order to clarify the situation, Table 7 presents the percentage of patients who experienced either a >7% weight increase or a >7% weight reduction by treatment duration(using an LVCF approach within each time period). In addition, the mean weight change by treatment duration is presented. (The data in Table 1 are based on the original data presented in the dossier).

Table 1 Weight data in patients treated with quetiapine in the Phase II/III controlled and uncontrolled trials

Treatment duration	N	% of patients			Mean weight change (kg)
		>7% reduction in weight	No significant change in weight	>7% gain in weight	
5 to 6 weeks	778	3.7	74.8	21.5	2.08
6 months	1190	12.0	62.9	25.0	0.76
12 months	573	13.8	50.9	35.3	1.59
>12 months	346	16.8	42.7	40.4	2.00

As can be seen in Table 7, at week 6 there is a marked imbalance between the percentage of patients who have experienced a >7% weight increase and reduction. This reflects the pharmacological effect of quetiapine. However, after this short-term effect, the increases in each category are more balanced reflecting the natural variability of weight across time.

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

APPLICATION FOR MARKETING AUTHORISATION

Response to comments made by the French Medicines Agency (FMA) in Annexe B of their letter dated 9 April 1998

June 1999

The uncertainty regarding the efficacy should be balanced with the undesirable effects, ie, hepatocytolysis (ALT > 5 x ULN in 0.4% of subjects), opacities on the lens, weight gain in 15% to 20% of subjects (2.8 kg in 6 months and 5 kg after 6 months) and neutropenia (4 to 5 per 1000).

AstraZeneca response (to weight gain):

The Commission commented that between 15% and 20% of patients had an increase in body weight of >7%. Table 6-8 provides data from the updated safety database.

Table 6-8 Magnitude of effect over time of quetiapine on weight gain in the Phase-II/III trials

Duration of exposure	Controlled trials (Mean duration 48.1 days)		Controlled and uncontrolled trials (Mean duration 164.4 days)	
	Number (%) with >7% the baseline weight	Total mean weight increase (kg)	Number (%) with >7% the baseline weight	Total mean weight increase (kg)
≤1 week	11 of 396 (2.8)	0.39	15 of 564 (2.7)	0.15
>1 to 2 weeks	38 of 475 (8.0)	0.67	45 of 661 (6.8)	0.64
>2 to 3 weeks	50 of 350 (14.3)	1.54	60 of 475 (12.6)	1.08
>3 to 4 weeks	48 of 338 (14.2)	1.65	62 of 495 (12.5)	1.20
>4 to 5 weeks	50 of 236 (21.2)	2.31	53 of 308 (17.2)	1.66
>5 to 6 weeks	164 of 727 (22.6)	2.19	167 of 778 (21.5)	2.08
>6 weeks to 6 months	61 of 289 (21.1)	1.55	337 of 1190 (28.3)	0.76
>6 to 12 months	34 of 66 (51.5)	5.15	229 of 573 (40.0)	1.59
>12 months	4 of 8 (50.0)	5.30	180 of 346 (52.0)	2.00
At any time	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

There was a duration-related increase in the incidence of clinically significant weight gain (>7% of baseline) in patients treated with quetiapine. The number of patients treated with quetiapine in the controlled and uncontrolled Phase-II/III trials who had an increase in body weight of >7% of baseline at any time during treatment (610 of 2216 [27.5%]) was higher than that at the end of

treatment (430 of 2216 [19.4%]), indicating that patients who had put on weight could subsequently lose it on continued quetiapine therapy.

The Commission commented that weight gain was 2.8 kg in the first 6 months and 5 kg after 6 months. Data from the updated safety database indicate that the mean greatest weight increase was 5 to 6 kg, and was higher in patients treated with quetiapine in the controlled trials compared with those in the combined controlled and uncontrolled trials. It should be noted that the number of patients in the controlled trials at the later time points is small, thus making it difficult to assess whether the increase in weight continues at the same rate or whether it slows after about 6 months.

Table 6-9 shows the mean weight increase and the incidence of clinically significant weight increases (>7% of baseline) by dose of quetiapine in the updated safety database.

Table 6-9 Number (%) of patients with clinically significant increase in body weight (>7% of baseline) by dose of quetiapine in the Phase-II/III trials

Dose of quetiapine	Controlled trials (Mean dose 342.3mg/day)		Controlled and uncontrolled trials (Mean dose 377.4mg/day)	
(mg/day)	Number (%) with >7% the baseline weight	Mean weight increase (kg)	Number (%) with >7% the baseline weight	Mean weight increase (kg)
<150	43 of 352 (12.2)	0.39	34 of 298 (11.4)	-0.18
≥150 but <300	51 of 276 (18.5)	1.51	129 of 466 (27.7)	1.37
≥300 but <450	95 of 498 (19.1)	1.49	169 of 623 (27.1)	1.30
≥450	106 of 422 (25.1)	2.23	274 of 822 (33.3)	0.09
Any dose	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

The mean weight change in patients in each group was small, although there was some evidence of a dose-related increase in incidence of patients gaining >7% of baseline in body weight.

In summary, these additional data confirm the findings in the original MAA and are consistent with the wording in the Summary of Product Characteristics, which states that treatment with quetiapine is sometimes associated with increases in body weight.

Response to the letter from the IKS (Interkantonale Kontrollstelle fur Heilmittel) dated 17 April 1997 concerning quetiapine tablets 25, 100 and 200 mg

September 1998

5 **The level of weight gain (22% of patients gained more than 7% in weight) was clearly higher than that observed for the standard preparation haloperidol. Sedation and autonomic, anticholinergic effects were more frequent than with the reference preparation. Where investigated, there was also a clear increase in serum cholesterol levels.**

5.1 Effect of quetiapine on weight gain

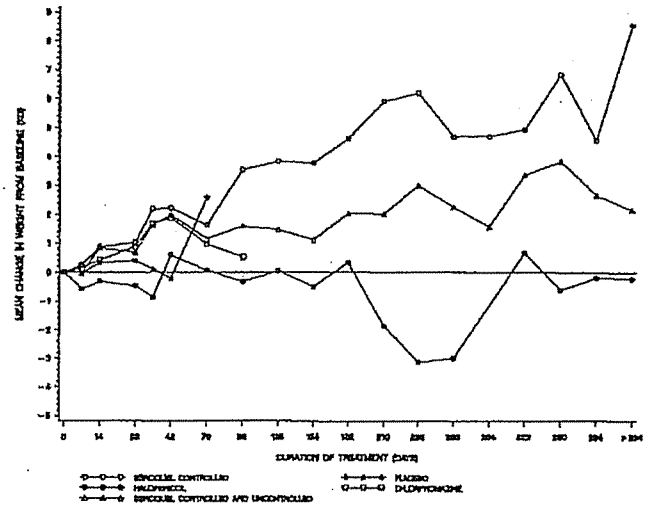
Supporting data are provided in the Supporting Documentation on the Safety of Quetiapine, Section 1.7.

As with most other antipsychotic agents - including recently approved agents such as olanzapine and risperidone - quetiapine was associated with weight gain.

The incidence of adverse events of weight gain in patients treated with quetiapine in the placebo-controlled trials was small (2.0% of 510) and lower than that in patients treated with olanzapine in similarly designed placebo-controlled trials (5.6% of 248). Patients treated with quetiapine in the placebo-controlled trials gained a mean of approximately 2 kg body weight, similar to that observed with olanzapine (2.8 kg; US Summary Basis of Approval for olanzapine).

The incidence of clinically significant weight increase (>7% of baseline) in patients treated with quetiapine in the Phase-II/III trials increased with time, suggesting that weight gain may be a manifestation of successful long-term treatment with quetiapine. Figure 2 shows the mean change in body weight over time in the Phase-II/III controlled and uncontrolled clinical trials.

Figure 2 Mean change in body weight by duration of therapy in the Phase-II/III trials



The proportion of patients who gained >7% body weight during quetiapine therapy appeared to increase with increasing dose; this may have been because patients tended to take high doses of quetiapine for longer periods than low doses.

The present wording in the section on 'Possible adverse reactions' in the Quetiapine SmPC adequately alerts the prescriber to the above findings in the clinical trials programme for quetiapine.

REPLY TO INSTRUCTIONS FROM IST MHW EVALUATION CENTRE (EC) HEARING

Seroquel 25/100 mg tablets

March 1999

Instruction 82

Make comments on a possible mechanism of hyperplasia of the glucagon-secreting cells in the pancreas and clinical relevance of this finding.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson et al 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate. In addition, the plasma prolactin levels did not increase in clinical studies. Therefore, the risk for human could be low.

References

Sorenson et al. Endocrinology 1995; 136: 4092-8.

Weinhaus et al. Endocrinology 1996; 137: 1640-9.

APPLICATION FOR MARKETING AUTHORISATION APPROVAL IN SWEDEN

Response to the Medical Products Agency's (MPA's) Assessment Report of 27 January 1997 concerning quetiapine (SEROQUEL™) tablets 25, 100 and 200 mg (Aspnr: 96-243, 96-244, 96-245)

February 1997

The mechanism of the hyperplasia of the glucagon secreting cells in the pancreas in the 1-year rat study should be discussed.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson and Stout 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate.

EXHIBIT 27

Unknown

From: Geller, Wayne
Sent: Wednesday, December 05, 2001 1:01 PM
To: Patridge, Melissa
Subject: RE: Metabolic issues

Thanks a lot Melissa

-----Original Message-----
From: Patridge, Melissa
Sent: Wednesday, December 05, 2001 12:46 PM
To: Geller, Wayne
Subject: RE: Metabolic issues

On December 4, 2001 a search was performed on ClinTrace for cumulative Seroquel reports of HLTs Diabetes mellitus (all forms) and Hyperglycaemic conditions NEC.

A total of 47 reports were noted. The earliest Sponsored study report was initially reported on April 5, 1994. There were eight reports including concomitant disease of diabetes. Of these, five reports were from spontaneous reporters, three were from sponsored studies and one was a literature report.

There were 39 reports that did not include reference to history of diabetes. Of these, eight were from sponsored studies, four from literature and the remaining were spontaneous reports.

-----Original Message-----
From: Geller, Wayne
Sent: Tuesday, December 04, 2001 1:48 PM
To: Patridge, Melissa
Subject: RE: Metabolic issues

M,

From the begining of history through November 30, 2001 please.

Thanks,
Wayne

-----Original Message-----
From: Patridge, Melissa
Sent: Tuesday, December 04, 2001 12:18 PM
To: Geller, Wayne
Subject: RE: Metabolic issues

Please clarify timeframes.

Marketed September 1997 and Clinical (date of first report)?

-----Original Message-----
From: Geller, Wayne
Sent: Tuesday, December 04, 2001 9:02 AM
To: Patridge, Melissa
Subject: FW: Metabolic issues

M.

Please do a BO search for the number of reports of Diabetes or hyperglycemia and provide me with just a number. Include both clinical and postmarketing timeframes.

Thanks,
Wayne

-----Original Message-----
From: Olbrich, Richard
Sent: Tuesday, December 04, 2001 3:35 AM
To: Hagger, Simon; 'carole.nadin@btinternet.com'; Geller, Wayne
Cc: Aked, Dominic M; Owen, Richard T; Ney, Christine A; Brecher, Martin; Lapp, Carrie
Subject: RE: Metabolic issues

Simon I agree with Wayne's proposal.

Wayne I'd like to be able to revise DOF 89 accordingly. Once you get the information from Carrie could you please let me know and send me DOF 89 with your suggested revisions.

Kind regards Richard

Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

-----Original Message-----
From: Hagger, Simon
Sent: Monday, 03 December, 2001 21:12
To: Olbrich, Richard; 'carole.nadin@btinternet.com'
Subject: FW: Metabolic issues

Hi both,
What do you think to Waynes suggestion below as a way forward? I'm happy with it if it can be worked out and done this way.
Thx
Simon

-----Original Message-----
From: Geller, Wayne
Sent: Monday, December 03, 2001 3:38 PM
To: Hagger, Simon
Subject: RE: Metabolic issues

Dear Simon,

My preference would be to provide incidence rates derived from comparative clinical trial data where the numerator and denominator are both known, and not estimates. If this is not possible, I would propose something similar to what Dom is proposing below, except it is important to understand that we are calculating a reporting rate which is far less accurate than (and can not be used in comparison to) a true incidence rate. Instead of providing reporting rates in absolute numbers, I would suggest using something similar to the CIOMS definitions:

Kind regards,
Wayne

-----Original Message-----
From: Hagger, Simon
Sent: Monday, December 03, 2001 3:09 PM
To: Geller, Wayne
Subject: FW: Metabolic issues

Hi Wayne,
please see Dominic Aked's response to my question over the metabolic data issue. Do either of the approcahes seem a reasonable compromise? I'd appreciate your thoughts.
Kind regards
Simon

-----Original Message-----
From: Aked, Dominic M
Sent: Thursday, November 29, 2001 5:28 AM
To: Hagger, Simon; Bowen, Rebecca
Cc: Owen, Richard T
Subject: RE: Metabolic issues

Hi Simon

I agree that presenting absolute figures will cause problems as they will need to be constantly updated.

We could consider presenting an estimate of the incidence, based on projected usage from sales. This might say something like.....

Post-marketing surveillance suggests the incidence of ??? glucose dyregulation associated with Seroquel is rare/infrequent (less that 0.??1%)

We would need to make assumptions about patient usage

Alternatively, we could stay with the data from placebo controlled trials.

Wayne's input is essential

Kind regards

Dom

-----Original Message-----
From: Hagger, Simon

Sent: Tuesday, 27 November, 2001 20:05
To: Aked, Dominic M; Bowen, Rebecca
Subject: FW: Metabolic issues

Dear Rebecca and Dom,
Please can you comment on the attached message from Wayne Geller concerning updating a DOF on metabolic issues from which we took data from post-marketing data from the FDA. How do you feel we should proceed bearing in mind Waynes comments? I would suggest we look at the impact of the DOF with this data removed.
Regards
Simon

-----Original Message-----
From: Geller, Wayne
Sent: Monday, November 26, 2001 11:13 AM
To: Olbrich, Richard; Hagger, Simon
Cc: Owen, Richard T
Subject: RE: Metabolic issues

Dear Richard and Simon,

The November 2000 discussion document on glucose dysregulation included the following numbers of events based on a data cut-off of October 2000:

"A search was conducted for all cases in which diabetes mellitus, hyperglycemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases".

The numbers provided here are out of date as there have been additional reports of DM and related maladies that have been received since October 2000. In addition, there has been considerable discussion of this in the literature. Caution should always be exercised in presenting any number of postmarketing adverse events as the number will increase over time and the number of events is likely to not represent the true number of events of that type due to underreporting and other biases. I am not keen on sharing numbers of postmarketing events and would suggest that you not do so either.

Kind regards,
Wayne

-----Original Message-----
From: Carole Nadin [mailto:carole.nadin@btinternet.com]
Sent: Thursday, November 22, 2001 12:01 PM
To: Olbrich, Richard; Hagger, Simon; Geller, Wayne
Cc: rob.kite@cmc.co.uk; X:Patefield, Iain (External)
Subject: Re: Metabolic issues

Attached.
Carole
----- Original Message -----
From: "Olbrich, Richard" <Richard.Olbrich@astrazeneca.com>
To: "'Carole Nadin'" <carole.nadin@btinternet.com>; "Hagger, Simon" <Simon.Hagger@astrazeneca.com>; "Geller, Wayne" <Wayne.Geller@astrazeneca.com>
Cc: <rob.kite@cmc.co.uk>; "X:Patefield, Iain (External)" <Iain.Patefield@CMC-international.com>
Sent: Thursday, November 22, 2001 3:34 PM
Subject: RE: Metabolic issues

Carole many thanks for your comments. Please resend the attachment as I've not received it. Wayne could you please comment on this. I enclose DOF 89 for your reference.

Kind regards Richard
Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

-----Original Message-----
From: Carole Nadin [mailto:carole.nadin@btinternet.com]
Sent: Wednesday, 21 November, 2001 16:17
To: Olbrich, Richard; Hagger, Simon
Cc: rob.kite@cmc.co.uk; X:Patefield, Iain (External)
Subject: Re: Metabolic issues

Dear Richard and Simon

This would be quite a significant change to the DoF and to the slides, as it more than doubles the number of spontaneous reports of diabetes. Would you mind double-checking it, please, before we change the slides and the DoF? The source of the data in DoF 89 was page 26 of the FDA response document (dated August 2000), which stated that there had been 12 reports of diabetes mellitus up to May 2000. This document was presumably quite thoroughly data-checked, and is also dated later than the presentation that Wayne Geller refers to (June 2000). As he said he did not know the source of the 12 cases figure, I attach a copy of the source document.
Could you ask him to confirm that the 12 cases figure is definitely wrong, please, and that it should definitely be replaced with his figure of 27 cases? Is it possible that there could be some difference in definition between the figure of 12 cases in the FDA document and the figure of 27 cases from Wayne Geller?
If it is confirmed that the figure in the DoF should be changed, could you also send me the relevant analysis that is the source of the 27 cases figure, please? Chip will need to sign off again, so I will need to tell him in the covering note what has changed and why.
Regards
Carole
----- Original Message -----
From: "Olbrich, Richard" <Richard.Olbrich@astrazeneca.com>
To: "Geller, Wayne" <Wayne.Geller@astrazeneca.com>;
<carole.nadin@btinternet.com>
Cc: "Owen, Richard T" <Richard.Owen@astrazeneca.com>; "Brecher, Martin"
<martin.brecher@astrazeneca.com>; "Ney, Christine A"
<christine.ney@astrazeneca.com>; "Rice, Moira M"
<Moira.Rice@astrazeneca.com>; "Hagger, Simon"
<Simon.Hagger@astrazeneca.com>; "Swalley, Jeffrey S"
<jeffrey.swalley@astrazeneca.com>; "Stening, Göran K"
<Goran.K.Stening@astrazeneca.com>; "Sayce, Rod" <Rod.Sayce@astrazeneca.com>;
"Dev, Vikram J" <vikram.dev@astrazeneca.com>; "Aked, Dominic M"

<Dominic.Aked@astrazeneca.com>
Sent: Tuesday, November 20, 2001 4:49 PM
Subject: RE: Metabolic issues

Wayne thanks for pointing this out.

Carole could you please amend DOF 89 to state 27 cases as opposed to 12 and also update the weight slide kit which also contains this incorrect information.

Kind regards Richard
Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

> -----Original Message-----
> From: Geller, Wayne
> Sent: Tuesday, 20 November, 2001 16:23
> To: Olbrich, Richard
> Cc: Owen, Richard T; Brecher, Martin; Ney, Christine A; Rice, Moira M;
> Hagger, Simon; Swalley, Jeffrey S; Stening, Göran K; Sayce, Rod; Dev,
> Vikram J
> Subject: RE: Metabolic issues
>
> Dear Richard et al,
>
> In response to your question below, I have not had an in depth look at
> either DM or hyperlipidemia recently. We have been tied-up with other
> issues and intend to have another look at these issues when we are able to
> do so. I do have a comment about the following statement which appears
> below (in this e-mail):
>
> Seroquel - extremely low incidence of diabetes
> mellitus
> (post-marketing data)
> * Approximately 623 000 patients received Seroquel between launch in
> the US (1997) and May 2000
> * Only 12 cases of diabetes mellitus reported
>
>
> This figure (12 reports of DM) is incorrect, and I don't know the source
> of this data. DM was presented at SERM in June 2000 with a data cut-off
> of May 2000. Through that time, there were 27 reports of diabetes
> mellitus and 2 reports of hyperglycemia received by AstraZeneca.
>
> Kind regards,
> Wayne
> -----Original Message-----
> From: Olbrich, Richard
> Sent: Tuesday, November 20, 2001 4:18 AM
> To: Sayce, Rod
> Cc: Owen, Richard T; Brecher, Martin; Geller, Wayne; Ney,

> Christine A; Rice, Moira M; Hagger, Simon; Swalley, Jeffrey S; Stening,
> Göran K
> Subject: RE: Metabolic issues
>
> Rod thanks for the note. Just to clarify I presume that you are
> suggesting that we publish on 'metabolic issues' which includes diabetes,
> weight and lipids? . We'd be defining metabolic issues as diabetes, weight
> and lipids - Martin do you agree?
>
> I agree that we would approach Goran's team to ask for the analysis.
>
> However before we do this I'd like to be clear as to exactly what we
> would want to 'claim' from the publication as this will drive Goran's
> analysis: for example do we want to say:
>
> 1. Seroquel is not associated with diabetes or its exacerbation.
> 'A review of the controlled clinical trials and the post marketing
> safety data base resulted in no statistically significant adverse effects
> of Seroquel with insulin levels, blood glucose leves or the incidence of
> diabetes.' (similar to DOF 89 and the reg defence document).
>
> 2. Seroquel does not adversely affect cholesterol, LDL,
> triglycerides
> 'A review of the controlled clinical trials and the post marketing
> safety data base resulted in no statistically significant adverse effects
> of Seroquel on cholesterol, LDL and triglycerides.
>
> 3. Although it is widely accepted that the the atypical
> antipsychotics have the same efficacy, Seroquel has the best tolerability.
> 'A review of the literature has shown widespread acknowledgment that
> the atypicals have similar efficacy. [I'm not sure how else we'd put this
> in the absence of direct head to head's with Seroquel] This paper has
> shown that Seroquel has an excellent tolerability profile, not only does
> it have placebo levels of EPS across the dose range, has no prolactin
> elevation and is weight neutral, but Seroquel has no metabolic issues* '
>
> *diabetes and lipids
>
> Wayne have you looked at diabetes and lipids?
> Martin would you like to add to the above?
>
>
> Kind regards Richard
> Richard Olbrich PhD
> Medical Affairs Manager- Seroquel
> PS&L
> AstraZeneca
> Alderley House Alderley Park
> Macclesfield Cheshire SK10 4TF
> United Kingdom
> Tel: +44 (0) 1625 515219
> Fax: +44 (0) 1625 515682
> Email richard.olbrich@astrazeneca.com
>
>
> -----Original Message-----
> From: Sayce, Rod
> Sent: Monday, 19 November, 2001 21:06
> To: Olbrich, Richard
> Cc: Owen, Richard T
> Subject: RE: Metabolic issues
>

> Dear Richard,
>
> Thanks for this. I believe that we have enough material for
> a review of the diabetes issue alone, without all the other parameters.
> However, without going overboard I think we could make a case for a review
> of the metabolic parameters for quetiapine - separately, CMC have
> suggested a safety update looking at all adverse events.
>
> Are you aware of any analyses that we have done looking at
> lipids? I know we have material that CMC are preparing at the moment on
> prolactin. Are we doing too much if we include this?
>
> I guess the next step will be to ask Goran's team to provide
> us with additional analysis - or is that up to Russell Giddins to provide?
> I presume Wayne Geller will also need to be involved at some point? I will
> then forward the information to CMC to start producing an outline of what
> we might want.
>
> I think Lou Aronne would be good if we focus on the weight
> issue, but I would like to see a diabetologist involved - my first point
> of contact would be John Buse of Chapel Hill, North Carolina, or Julio
> Rosenstock (Dallas, Texas) to identify someone who might be interested in
> helping us with the manuscript. If we are going to include a lot of lipid
> data, we might want to go to a cardiologist as well REDACTED
> REDACTED
>
> Would appreciate your thoughts ...
>
> Thanks,
>
> Rod
>
> -----Original Message-----
> From: Olbrich, Richard
> Sent: Friday, November 16, 2001 10:29 AM
> To: Sayce, Rod
> Subject: RE: Metabolic issues
> Importance: High
>
> Rod yes I did receive it please find enclosed:
>
> << Message: FW: regulatory defence document for
> diabetes >>
>
> Kind regards Richard
> Richard Olbrich PhD
> Medical Affairs Manager- Seroquel
> PS&L
> AstraZeneca
> Alderley House Alderley Park
> Macclesfield Cheshire SK10 4TF
> United Kingdom
> Tel: +44 (0) 1625 515219
> Fax: +44 (0) 1625 515682
> Email richard.olbrich@astrazeneca.com
>
>
> -----Original Message-----
> From: Sayce, Rod
> Sent: Friday, 16 November, 2001 15:26
> To: Olbrich, Richard
> Cc: Owen, Richard T

> Subject: Metabolic issues
>
> Dear Richard,
>
> I discussed this briefly during the COT, and on
> returning to work (at home today), I realize that I have not received a
> copy of the regulatory defence document - can you tell me if you ever
> received a copy? If not, I can chase up with Wayne on Monday.
>
> Many thanks,
>
> Rod
>
> -----Original Message-----
> From: Aked, Dominic M
> Sent: Saturday, September 15, 2001 4:57 AM
> To: Sayce, Rod; Hagger, Simon; Fitton, Lesley R
> Cc: Oldham, Alex; Brecher, Martin; 'Rebecca
> Bowen (E-mail)'; Holdsworth, Debbie; Owen, Richard T; Olbrich, Richard;
> Rice, Moira M
> Subject: RE: Dom re: metabolic issues
>
>
> Hi Rod, Simon and Lesley
>
> Can we discuss the proposed publication by Martin,
> and how we move this forward. I'll ask Alwyn to set up a teleconference
> for early next week.
>
> Richard (Olbrich): could you please liase with Wayne
> Geller or Russell Giddins, and obtain a copy of the regulatory defence
> document for diabetes
> Richard (Owen): could you please work with Moira to
> obtain the relevant literature searches.
>
> Lesley we will need to look at the data base, so we
> will need your guidance on who can do this work.
>
> Thanks for your help
>
> Kind regards
>
> Dom
>
>
>
>
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 18:40
> To: Aked, Dominic M; 'Rebecca Bowen (E-mail)'
> Cc: Oldham, Alex; Olbrich, Richard; Owen,
> Richard T
> Subject: RE: Dom re: metabolic issues
>
> Dom,
> We should include data regarding choleaserol, LDL
> and triglycerides. I suspect we haven't reviewed this in a while. Please
> confirm. If need confirmed I'll ask Wayne to look at Clintrace and we
> would need Emma and Karen to look at trial data base. We will also need
> to do a comprehensive publication review. Also suggest we designate a

> senior writer to put it together and to put it towards the top of the todo
> list. We will also probably want a OL on the paper. None of the
> psychiatry OL's really know this area which is medical not psychiatric.
> Wirshing has published, but he's not predictable. Suggest we get a
> friendly endocrinologist or internist-perhaps Lou Aronne who was on the US
> obesity ad board last December. We probably also need to get Adam
> Richards on board too.
> Martin
>
> -----Original Message-----
> From: Aked, Dominic M
> Sent: Friday, September 14, 2001 6:51 AM
> To: Brecher, Martin; Rebecca Bowen (E-mail)
> Cc: Oldham, Alex; Olbrich, Richard; Owen,
> Richard T
> Subject: Dom re: metabolic issues
> Importance: High
>
> Hi Martin
>
> Some thoughts.
>
> I strongly expect Janssen will drive this message in
> their marketing activities, as it delivers clear differential advantage
> over Zyprexa. We will need to counter this, as customers will want to
> make a comparison amongst the atypicals.
>
> The need to monitor blood glucose is also being
> debated, which could greatly influence doctors' prescribing.
>
> Therefore, I agree addition communications (e.g.
> publication as you suggest) would be helpful
>
> The data/messages we have been working with to-date
> are highlighted below. These data are as compelling as the Risperidal
> data, and therefore it is hoped that the marketing companies are
> responding to Janssen messages in the 'market place'. Perhaps we could
> raise the awareness of the MCs on this subject, and ask the top 10 (?) MCs
> what the situation is in their markets. These e-mails could form teh basis
> of a communication from one of teh GBMs (Simon?).
>
> We (the MAMs) will look at the regulatory defence
> document to see if there is anything more we can use promotionally.
>
> Kind regards
> Dom
>
> General information on diabetes
> * In the general population, the NHIS 1994 diabetes rate was 1.2% for
> persons aged 18-44 and 6.3% for persons aged 45-64
> * In patients with schizophrenia, 9-14% have current treated diabetes
>
> Seroquel - extremely low incidence of diabetes
> mellitus
> (post-marketing data)
> * Approximately 623 000 patients received Seroquel between launch in
> the US (1997) and May 2000
> * Only 12 cases of diabetes mellitus reported
>
> Seroquel - low incidence of adverse events possibly
> related to changes in glucose metabolism
>

>
> << File: weight change new.ppt >> << File:
> Weight gain.doc >>
> Seroquel is not associated with diabetes or its
> exacerbation
>
> << File: DoF AZ_S089.doc >>
> Number and percentage of Seroquel-treated patients
> in short-term controlled Phase II/III clinical trials with adverse events
> possibly related to changes in glucose metabolism.
> Seroquel N=1450 Placebo
> N=206 Haloperidol N=279 Clorpromazine N=100
> Diabetes melitus 0% 0%
> 0% 0%
>
> Number and percentage of Seroquel-treated patients
> in long-term controlled Phase II/III clinical trials with adverse events
> possibly related to changes in
> glucose metabolism.
> Seroquel n=260 Haloperidol
> n=41
> 0% 0%
>
>
> Janssen are making the following claims:
>
> Incidence of diabetes <1%
> Double blind trials Risperidal 0.0%
> Placebo 0.0%
> n=1838
> n=195
>
> Double blind + Risperidal 0.2% N/A
> open-label trials n=2607
>
> No need for serum glucose monitoring
>
>
> Diabetes: a concern with seleected newer
> antipsychotics
> * Occurs with or without weight gain
> * Occurs regardless of family history
> * Up to 50% of people with type 2 diabtetes are undiagnosed
> * Short and long-term health complications from diabetes: skin
> infections; retinopathy/cataracts; cadiovascular disease; increased
> mortality risk
> Evaluate diabetes risk of selected antipsychotics
>
> Adverse events reported since market introduction
> that were temporally (but not necessarily) related to Risperidal therapy
> include diabetes mellitus aggravated, including diabetisc ketoacidosis.
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 03:39
> To: Aked, Dominic M; Bowen, Rebecca
> Cc: Oldham, Alex
> Subject: metabolic issues
>
> << Message: Seroquel Pre-SERM Information >>
> Dom, Rebecca,
> 2 small streams of information have come my way.

> First is an advertisement from a psych journal from Janssen claiming no
> diabetes with risperidone. Second is a bibliography received yesterday
> (attached) with includes abstacts of several articles characterizing small
> patient samples in which clozapine and olanzapine had adverse effects on
> cholesterol, LDL, triglycerides, insulin levels, blood glucose and the
> incidence of diabetes. Quetiapine as best I can tell from the abstracts
> comes off as a lesser offender. Risperidone is not linked to these
> events. I therefore would like your views whether we should do a review
> of our data designed to lead to a publication where we add no adverse
> metabolic consequences to our preferred safety profile along with EPS,
> prolactin weight and QT.
> We have already submitted a regulatory defense
> showing no effect of Seroquel on random blood glucose and no signal of new
> diabetes or hyperglyemia.
> Trials 41 (SR pivotal) and 43 (risperidone
> comparator) measure fasting blood glucose and trial 43 also measures
> fasting cholesterol, LDL and triglycerides.
> To rephrase the question, Is there a perception of a
> clinical issue on metabolism with Seroquel and do we need to try to put a
> stake in the ground as soon as possible and in advance of the Trial 43
> data?
> Thanks
> Martin
>
> PS I wrote this prior to reading your mail regarding
> the Semyak, Wilson (included among the refs) and Casey posters which are
> consistent with the data cited above.
>
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 03:39
> To: Aked, Dominic M; Bowen, Rebecca
> Cc: Oldham, Alex
> Subject: metabolic issues
>
> << Message: Seroquel Pre-SERM Information >>
> Dom, Rebecca,
> 2 small streams of information have come my way.
> First is an advertisement from a psych journal from Janssen claiming no
> diabetes with risperidone. Second is a bibliography received yesterday
> (attached) with includes abstacts of several articles characterizing small
> patient samples in which clozapine and olanzapine had adverse effects on
> cholesterol, LDL, triglycerides, insulin levels, blood glucose and the
> incidence of diabetes. Quetiapine as best I can tell from the abstracts
> comes off as a lesser offender. Risperidone is not linked to these
> events. I therefore would like your views whether we should do a review
> of our data designed to lead to a publication where we add no adverse
> metabolic consequences to our preferred safety profile along with EPS,
> prolactin weight and QT.
> We have already submitted a regulatory defense
> showing no effect of Seroquel on random blood glucose and no signal of new
> diabetes or hyperglyemia.
> Trials 41 (SR pivotal) and 43 (risperidone
> comparator) measure fasting blood glucose and trial 43 also measures
> fasting cholesterol, LDL and triglycerides.
> To rephrase the question, Is there a perception of a
> clinical issue on metabolism with Seroquel and do we need to try to put a
> stake in the ground as soon as possible and in advance of the Trial 43
> data?
> Thanks
> Martin

Read it - Trial 41?

>
> PS I wrote this prior to reading your mail regarding
> the Semyak, Wilson (included among the refs) and Casey posters which are
> consistent with the data cited above.

EXHIBIT 28

Clinical Study

The weight profile of SEROQUEL over the long term

Authors: Brecher M, Rak IW, Melvin K, et al.

Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

Journal: *International Journal of Psychiatry in Clinical Practice*. 2000;4:287-291.

Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - 178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

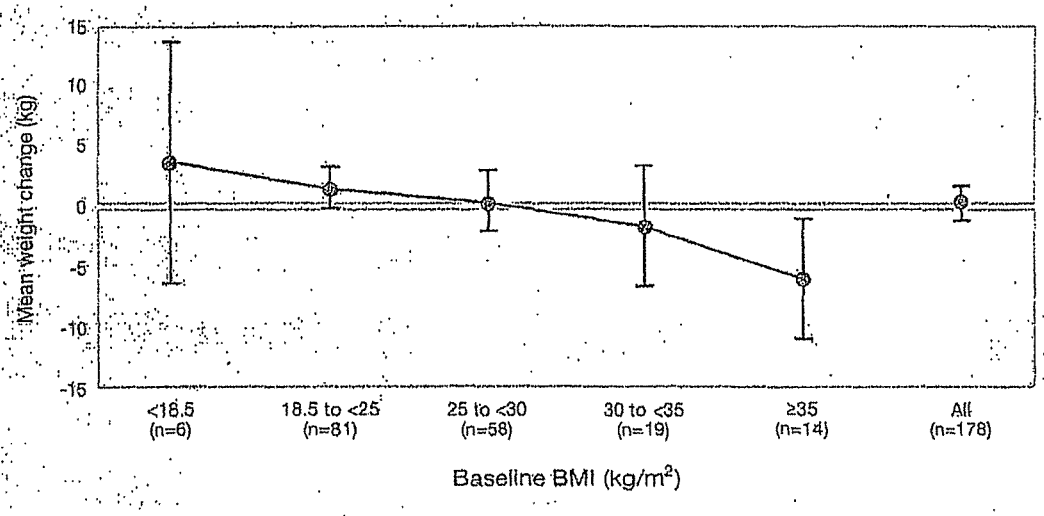
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*Final recorded weight measurement.

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

M BRECHER,[1] IW RAK,[1] K MELVIN[2] AND AM JONES[2]

AstraZeneca, [1]Wilmington, DE, USA and [2]Alderley Park, Macclesfield, Cheshire, UK

Correspondence Address
Dr Martin Brecher, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE, USA
Tel: +1 (302) 886 2634
Email: martin.brecher@astrazeneca.com

Received 2 May 2000; revised 3 November 2000; accepted for publication 3 November 2000

INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 kg/m^2) and severely obese patients (BMI ≥ 35 kg/m^2).

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[4] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Seroquel is a trademark, the property of the AstraZeneca Group of Companies.

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
≤50 kg	53
50–70 kg	171
71–90 kg	164
>90 kg	59

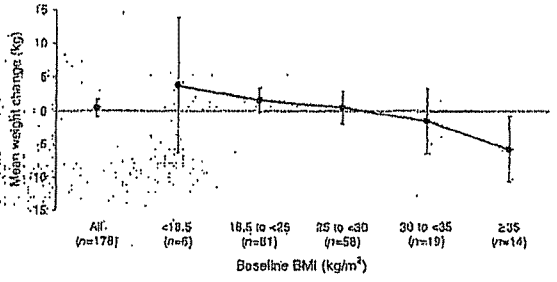


Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg.

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

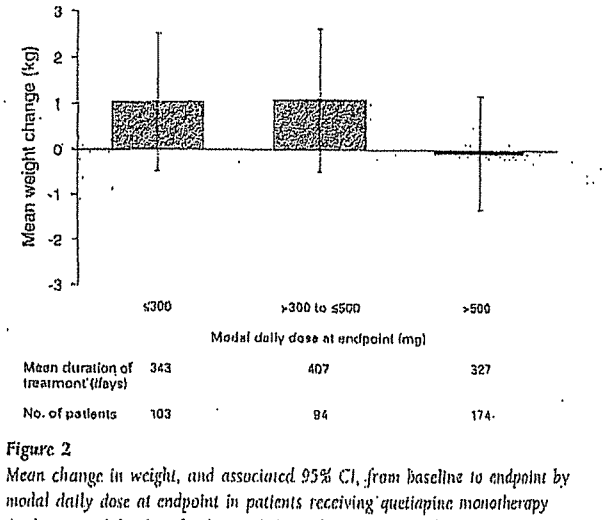


Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m²)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5 <25	81	468	539	1.6
≥25 <30	58	466	607	0.53
≥30 <35	19	514	551	−1.53
≥35	14	493	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,18,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably.
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m²), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender.
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients.
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.

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EXHIBIT 29

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

November 2002
NO. 02-5

Dear Dr. Letter

Diabetic ketoacidosis and diabetic coma due to an increase in blood glucose level during administration of Seroquel® 25mg, 100mg tablets (quetiapine), an antipsychotic drug

Since February 2001 when Seroquel was started to be marketed, 12 serious cases (including 1 death) of hyperglycaemia, diabetic ketoacidosis, and diabetic coma where causality with the drug could not be ruled out have been reported (estimated number of patients who used Seroquel of the end of September 2002 was approximately 130,000). Hyperglycaemia was added in the "Precautions for use" to call attention in July 2002; however, based on the discussion of serious cases, "Contraindication" and "Precautions for use" were revised, and "Warning" was added to the package leaflet. This drug should be cautiously administered with strict attention to the following instructions. If Adverse reaction as above is confirmed, please contact the person in charge of Drug Information of Fujisawa which is the marketing company for Japan.

Manufacturing company: AstraZeneca K.K.
Marketing company: Fujisawa Pharmaceutical Co. Ltd.

1. **Seroquel must not be administered to patients with diabetes or a history of diabetes.**

In diabetic patients or patients having a history of diabetes, blood glucose levels may elevate, which may rapidly aggravate metabolic conditions. This drug must not be given to such patients.

2. **During administration of Seroquel, the patient should be monitored carefully including measurement of blood glucose levels.**

During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration of the drug may cause serious adverse reactions such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.

3. **Information on the adverse reactions and action to be taken must be fully explained to the patient and the family.**

Prior to administration of the drug, sufficient explanation should be provided to the patient and the family that significant adverse reactions including diabetic ketoacidosis and diabetic coma may occur. They should be instructed to stop administration of the drug and visit hospital if any symptoms such as thirst, polydipsia, polyuria, increased urinary frequency or others appear.

"Warning", "Contraindication" and "Precautions for use" were revised on the underside of the leaflet.

Contact : Post-Marketing Surveillance 1, Fujisawa Pharmaceutical Co., LTD.
1-6, Kashima 2-Chome, Yodogawa-ku, Osaka, Japan, 532-8514
Phone: +81-6-6390-5266
Fax: +81-6-6304-1319

(Narratives)
Not fixed

No.	Sex, age, reason for use [Complication]	Clinical course and treatment
1		
	Concomitant drugs:	
2		
	Concomitant drugs:	
3		
	Concomitant drugs:	
4		
	Concomitant drugs:	

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

Dear Dr. Letter

"Warning", "Contraindication" and "Precautions for use"

"Warning", "Contraindication" and "Precautions for use" were revised as follows. This revision is based on the post-marketing incidence of hyperglycaemia.

[Warning]

1. During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration may cause significant side effects such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.
2. Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency and also instructed to stop administration of the drug and visit hospital if any of these symptoms appear. [See "Important basic precautions"]

[Contraindication] The drug must not be given to the following patients.

5. Patients with diabetes or a history of diabetes

[Precautions for use]

1. Careful administration (The drug should be given with particular caution in the following patients.)

(6) Patients with a family history of diabetes, or those having diabetes risk factors such as hyperglycaemia or obesity [See "Important basic precautions"]

2. Important basic precautions

(1) Administration of the drug may markedly increase blood glucose, in some patients, leading to life-threatening clinical courses including diabetic ketoacidosis or

diabetic coma. During administration of the drug, blood glucose levels should be measured, and thirst, polydipsia, polyuria, increased urinary frequency and others should be fully monitored. Especially for the patients with diabetes risk factors such as hyperglycaemia or obesity, increased blood glucose may rapidly aggravate metabolic conditions.

(2) Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above serious side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency, and also instructed to stop administration of the drug if such a symptom may appear, and visit hospital.

(3) Administration of the drug may increase body weight. Pay attention to obesity, and if a sign of obesity is observed, appropriate action including diet therapy or exercise therapy should be taken.

3. Adverse Reactions

(1) Clinically significant adverse reactions

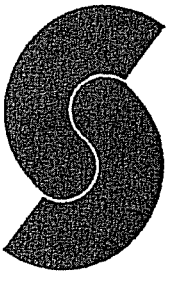
1) Hyperglycaemia, diabetic ketoacidosis, and diabetic coma: Hyperglycaemia may appear, and occurrence of diabetic ketoacidosis or diabetic coma may lead to life-threatening clinical courses. Measurement of blood glucose and observation of thirst, polydipsia, polyuria, and increased urinary frequency should be fully carried out. If any abnormalities are found, administration should be stopped, and appropriate action such as administration of insulin preparations should be taken.

(Only revised parts are described.)

EXHIBIT 3

AstraZeneca Pharmaceuticals

Seroquel™
(Quetiapine)



Commercial Support Team - Technical Document (TD005)

CGI - Severity of Illness Meta-Analysis

Request From: Debbie Holdsworth

Date Requested: Jan 2000

Statistician/Statistical Programmer Responsible: Rob Hemmings

1 Source of Data

This document summarises initial findings into a meta-analysis of CGI - Severity of Illnes (SoI) scores taken from trials 5077IL/0013, 14, 50 and 52. As with all meta-analyses, care is required in choosing which combinations of trials can sensibly be interpreted. The data below comprises all our comparative data with Haloperidol (with the exception of trial 5077IL/0015 which assessed a significantly different patient population) and as such combines slightly different patient populations, inclusion / exclusion criterion, timings of endpoints, and doses of drug. This seems acceptable however, in order look for a general claim of superior efficacy for Seroquel over Haloperidol with regards CGI - SoI.

Any analysis of this data would be post-hoc.

2 Design of Trials/ Analysis Methods

2.1 Study Design

Table 1 gives a summary of the trials used and the pertinent design features from each trial.

Table 1

TRIAL	Treatments / Dose (# pats.)	Patient population	Inc/Exc criteria	Timing of endpoint
52 (PRIZE)	SER 600mg/day BD HAL 20mg/day BD (330 in total, 1:1 rand)	Schiz. pats. with history of partial response to trad anti-psychotic therapies	CGI, SoI >= 3	8 weeks after baseline
50 (ESTO)	SER up to 600mg/day BD HAL up to 20mg/day BD (190 in each tmt group)	Patients presenting with acute exacerbation of schiz. or schiz. disorder in last 3 years	CGI, SoI >= 4	12 weeks after baseline (also 24 and 52 weeks after baseline)
14	SER up to 800 mg/day BD HAL up to 16 mg/day BD (220 per group)	Acute exacerbation of subchronic or chronic schiz.	CGI, SoI >= 4	6 weeks after baseline
13	SER 75, 150, 300, 600, 750 mg/day TD HAL 12 mg/day TD PLACEBO (50 pats. per arm)	Hosp. patients with acute exacerbation of chronic or sub-chronic schiz.	CGI, SoI >= 4	6 weeks after baseline

Points to note are:

- Differing doses of SER and HAL across the trials;
- Slightly different patient populations (especially 52);
- Differing times of endpoint assessment.
- Data from the 75mg/day group has been excluded from trial 0013 as it is not in the therapeutic dose range for Seroquel.

2.2 Analysis Methods

Only descriptive summaries have been performed on this combined data. The only assumption made is that results can be sensibly interpreted when data from these trials are combined.

2.3 Details of SAS programs

Analysis programs from trials 13 and 14 are stored in the CDE under the CST directory (s:\d5077\filesm\CST) in two programs named TD5_G1 and TD5_G2. Analysis programs from trials 50 and 52 are in the CDE under the trial directory and are named as above.

3 Results

Before the data from these trials was considered for analysis, they were explored using standard summary statistics. The endpoints requested to be explored were: Change from baseline in Severity of Illness; and Proportion of patients with Severity of Illness ≤ 3 at endpoint.

Table T1 (Appendix A) shows the results of these summaries. Using either endpoint definition, it is clear that a claim of superiority for Seroquel over Haloperidol could not be generated using these data as the Haloperidol arm has a greater proportion of patients with lower CGI-SoI at endpoint and with greater reductions from baseline. It is noted, however, that a claim of 'equivalence' may be possible, given a prospective definition of clinical equivalence limits.

It was feared that messages from these trials may have been diluted by combining low and high doses of Seroquel. Therefore data from trials 13, 14, 15 and 50 were further explored, by taking only the following data:

Table 2 - Definition of 'High' doses of Seroquel for each of the trials

TRIAL	mg/day	
13	>= 600	i.e. ignoring the 75, 150 and 300 mg/day categories
14	>= 450	
50	>=450	
52	600	i.e. all available data

Results from these additional explorations are summarised in table T2 Appendix A (in addition, dose response results from trial 13 is summarised in Appendix B below). They do not suggest any different conclusions to those described above, i.e. that a claim of superiority is highly unlikely using these definitions, whilst a claim of equivalence is not ruled out.

A final hypothesis examined was that the effect of Seroquel relative to Haloperidol may be larger in patients with severe disease at baseline. Tables T3 and T4 in Appendix A are repeats of table T1 but for patients with baseline severity of 3-5 and 6,7 respectively.

4 Conclusions

The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of equivalence is not ruled out.

5 References

None

Appendix A: Statistical Appendix

Index of Tables Created

TABLE T1 Change from baseline and level of severity at endpoint in CGI-SoI scores

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	1	0	2	0	0	0	0	0	3	0	0.4	0
-4	0	1	4	12	4	5	2	1	10	19	1.5	3.5
-3	9	2	20	25	17	18	5	5	51	50	7.5	9.3
-2	22	8	44	53	26	33	21	14	113	108	16.6	20.0
-1	63	13	68	58	60	54	35	35	226	160	33.3	29.6
0	82	22	49	55	30	39	34	54	195	170	28.7	31.5
1	22	4	30	9	9	5	11	7	72	25	10.6	4.6
2	5	0	2	7	0	0	1	1	8	8	1.1	1.5
3	0	0	1	0	0	0	0	0	1	0	0.1	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									679	540	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	2	0	5	8	6	4	3	3	16	15	2.4	2.8
2	14	5	29	33	10	20	15	8	68	66	10.0	12.2
3	39	7	53	52	38	42	35	31	165	132	24.3	24.4
4	58	16	46	58	55	44	36	46	185	164	27.2	30.4
5	44	14	42	36	26	36	10	21	122	107	18.0	19.8
6	47	5	35	28	9	7	9	7	100	47	14.7	8.7
7	10	3	10	4	2	1	1	1	23	9	3.4	1.7
									679	540	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

TABLE T2 Change from baseline and level of severity at endpoint in CGI-SoI scores (high doses of Seroquel only)

Change from baseline in severity	TRIAL 13		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	0	0	0	0	0	0	0	0	0	0	0	0
-4	0	1	0	12	2	5	2	1	4	19	1.3	3.5
-3	2	2	2	25	4	18	5	5	13	50	4.1	9.3
-2	13	8	14	53	5	33	21	14	53	108	16.9	20.0
-1	34	13	20	58	12	54	35	35	101	160	32.2	29.6
0	40	22	17	55	11	39	34	54	102	170	32.5	31.5
1	14	4	10	9	3	5	11	7	38	25	12.1	4.6
2	2	0	0	7	0	0	1	1	3	8	0.1	1.5
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									314	540	100	100

Level of severity at endpoint	TRIAL 13		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
				n			n	n	n	n	n	n
1	0	0	0	8	2	4	3	3	5	15	1.6	2.8
2	8	5	2	33	2	20	15	8	27	66	8.6	12.2
3	20	7	19	52	8	42	35	31	82	132	26.1	24.4
4	24	16	13	58	14	44	36	46	87	164	27.7	30.4
5	25	14	13	36	7	36	10	21	55	107	17.5	19.8
6	22	5	14	28	3	7	9	7	48	47	15.3	8.7
7	6	3	2	4	1	1	1	1	10	9	3.2	1.7
									314	540	100	100

TABLE T3 Change from baseline and level of severity at endpoint in CGI-SoI scores (patients with baseline score of 3, 4 or 5)

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	0	0	0	0	0	0	0	0	0	0	0	0
-4	0	0	2	5	3	4	2	1	7	10	1.3	2.4
-3	7	1	16	14	7	9	4	5	34	29	6.5	6.9
-2	19	6	38	39	15	26	18	13	90	84	17.3	20.0
-1	48	9	56	46	49	44	32	31	185	130	35.6	30.9
0	51	17	30	37	24	33	30	50	135	137	26.0	32.5
1	18	2	24	9	7	5	11	7	60	23	11.5	5.5
2	5	0	2	7	0	0	1	1	8	8	1.5	1.9
3	0	0	1	0	0	0	0	0	1	0	0.2	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									520	421	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	1	0	3	8	6	4	3	3	13	15	2.5	3.6
2	14	4	27	26	9	19	15	8	65	57	12.5	13.5
3	37	6	49	41	28	33	34	31	148	113	28.5	26.8
4	45	14	41	44	44	37	33	46	163	141	31.3	33.5
5	32	10	29	25	15	26	7	16	83	77	16.0	18.3
6	18	1	19	10	3	2	6	4	46	15	8.8	3.6
7	1	0	1	3	0	0	0	0	2	3	0.4	0.7
									520	421	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

TABLE T4 Change from baseline and level of severity at endpoint in CGI-SoI scores (patients with baseline score of 6,7)

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	1	0	2	0	0	0	0	0	3	0	1.9	0
-4	0	1	2	7	1	1	0	0	3	9	1.9	7.6
-3	2	1	4	11	10	9	1	0	17	21	10.7	17.6
-2	3	2	6	14	11	7	3	1	23	24	14.5	20.2
-1	15	4	12	12	11	10	3	4	41	30	25.8	25.2
0	31	5	19	18	6	6	4	4	60	33	37.7	27.7
1	4	2	6	0	2	0	0	0	12	2	7.5	1.7
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									159	119	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	1	0	2	0	0	0	0	0	3	0	1.9	0
2	0	1	2	7	1	1	0	0	3	9	1.9	7.6
3	2	1	4	11	10	9	1	0	17	21	10.7	17.6
4	3	2	5	14	11	7	3	0	22	23	13.8	19.3
5	12	4	13	11	11	10	3	5	39	30	24.5	25.2
6	29	4	16	18	6	5	3	3	54	30	34.0	25.2
7	9	3	9	1	2	1	1	1	21	6	13.2	5.0
									159	119	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

Appendix B: Supporting Presentations

TABLE T5 - CGI-Sol Trial 0013

Level of severity at endpoint	DOSE (mg/day) SER 150	SER 300	SER 600	SER 750	HAL 12	PLA
	n	n	n	n	n	n
1	0	2	0	0	0	0
2	1	5	7	1	5	1
3	14	5	8	12	7	3
4	9	15	10	14	16	11
5	9	10	13	12	14	16
6	13	12	8	14	5	12
7	2	2	5	1	3	8

Change from baseline in severity	DOSE (mg/day) SER 150	SER 300	SER 600	SER 750	HAL 12	PLA
	n	n	n	n	n	n
-5	0	1	0	0	0	0
-4	0	0	0	0	1	0
-3	3	4	2	0	2	0
-2	4	5	7	6	8	2
-1	13	16	14	20	13	7
0	23	19	19	21	22	24
1	3	5	7	7	4	13
2	2	1	2	0	0	5
3	0	0	0	0	0	0
4	0	0	0	0	0	0

Technical Document (TD005)

Approved for issue by:

Andrew Gorman
Project Team Physician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

Emma Westhead
Senior Statistician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

EXHIBIT 30

Objection Handler on
Atypical antipsychotics and glucose dysregulation

By Dr Richard Owen
Global Medical Affairs Manager-Seroquel

With contributions from: Rebecca Bowen (Global Brand Director)
Dr Chip Altman (Global Commercial Physician)
Alison Wilkie (Global Communications Manager

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Date issued : 26 November 2002 (version 1)

Summary

- **The literature contains much conflicting information concerning the prevalence of diabetes and glucose dysregulation with atypical antipsychotics. Most of the published evidence relates to clozapine and olanzapine.**

- **Product labels vary widely between countries concerning statements about diabetic risk-not only between products but for the same product in different countries.**

- **The company's safety database has reassuring data concerning Seroquel's diabetic potential and glucose regulation**

Background

Abnormalities in glucose regulation including diabetes mellitus can occur more commonly in schizophrenia patients compared with healthy individuals; a phenomenon which has been recognised even prior to the neuroleptic era. Hyperglycaemia, exacerbation of existing diabetes, new onset type 2 diabetes and diabetic ketoacidosis have been reported with a variety of atypical agents but the vast majority of reports are with clozapine and olanzapine.

This objection handler summarises the key publications in the literature to date, label statements and changes with our main competitors and summarises our data with Seroquel regarding diabetes and glucose dysregulation.

Summary of selected published data

A recent review by Henderson (CNS Drugs 2002; 16 (2): 77-89) reviews the evidence for atypical antipsychotic-induced diabetes mellitus.

Henderson.pdf

In summary their main conclusions was that most of the evidence of diabetogenic risk relates to clozapine and olanzapine. However the topic is complex and the literature is full of both supportive or dismissive evidence concerning the risk of hyperglycaemia and diabetes with atypicals. Only controlled trials will lead to a fuller understanding and such trials are at present uncommon.

It is interesting to note the different approaches by the various companies in relation to their antipsychotic. The approaches can be broadly summarised as follows:

Lilly- have tried to imply that diabetes/glucose dysregulation is a <u>class effect</u> of atypicals (in other words if olanzapine is going to be singled out as a culprit they intend to brand all the atypicals as guilty as well)!

Janssen and *Pfizer*- tried to imply that risperidone and ziprasidone are different to other atypicals in that it cause little or no problems with diabetes or glucose regulation. (Data cited in Henderson 2002). Moreover risperidone has been used without complications in patients with schizophrenia and comorbid diabetes.

BMS- have published retrospective audits showing that olanzapine and risperidone are associated with increased diabetic risk compared to typicals (but surprisingly did not mention their own drug aripiprazole in this audit).
See e.g. BMJ article by Koro et al 2002-11-22
Koro et al 2002
They have shown relatively little data on aripiprazole and glucose levels although data on fasting blood glucose levels from a 26 week study did not reveal any problems (see CME slide no.58 in Key Claims section in the aripirazole pyramid).
http://cns.ta.astrazeneca.net/pyramids/Aripiprazole/aripiprazole_Claims.htm

AZ- We have presented data on an audit by Gianfrancesco et al showing that the risk with olanzapine is greater than the risk with Seroquel, risperidone and conventional antipsychotics.
Gianfrancesco et al 2002
There are data from Reinstein et al (Clin Drug Invest. 1999; 18: 99-104) showing that the addition of Seroquel to a clozapine regime improved glucose metabolism in 20% of the 13 patients who developed diabetes on clozapine alone. We currently await the results of study 43 which will compare fasting blood glucose levels between Seroquel and risperidone.

A selection of recent literature on diabetes and antipsychotics is attached.


Rev-lit-diab.doc

Label statements/changes that have occurred for Seroquel and the competition

(a) Japan

Recently the Japanese regulatory authorities imposed label changes relating to diabetes and glucose dysregulation for both Zyprexa (in April 2002) and Seroquel(in November 2002). These essentially comprise a contraindication for these agents in patients with diabetes or a history of diabetes and a requirement for blood glucose monitoring. The attached icon contains details of the letter that was sent to clinicians in Japan explaining the change to the labelling.


Sero-japdeardr.doc

Risperidone recently had the word 'hyperglycaemia' added to the other ADR's section of its label in Japan. Clozapine aripiprazole and ziprasidone are not yet marketed in Japan.

(b) US

The table below gives the current US PDR classification of glucose related adverse events for marketed /soon to be marketed atypicals.

	Adverse event frequency	
Product	**Infrequent (0.1-1%)**	**Rare (<0.1%)**
Seroquel	Hyperglycaemia Diabetes mellitus	
Olanzapine	Diabetes mellitus Hyperglycaemia	
Aripiprazole	Diabetes mellitus Hyperglycaemia	
Risperidone	Diabetes mellitus	
Ziprasidone	Hyperglycaemia	Glucose tolerance decreased
Clozapine	Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of CLOZARIL® (clozapine) should be considered. Hyperglycaemia (<1%)	

(c) Europe

Seroquel

EU – the Pharmacovigilance Working Party of the CPMP reviewed the class in June 2001. Seroquel SmPC has language "Special Warnings and Precautions for Use" section stating that hyperglycaemia and exacerbation of preexisting diabetes has been reported in very rare cases and that appropriate clinical monitoring is advisable. Similar wording is also in the Undesirable Effects section.

In UK, discussions regarding these issues are pending with MCA and should be resolved by the end of the year

The Italian label includes warnings and precautions that hyperglycaemia and the exacerbation of pre-existing diabetes have been reported rarely, and that monitoring is advisable.

Olanzapine

The EU label for olanzapine states that elevated glucose levels are common (frequency 1-10%). In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels <7.8 nmol/l the incidence of non-fasting plasma glucose levels >11nmol/l (suggestive of diabetes) was 1.0% compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels >8.9nmol/l but <11mmol/l (suggestive of hyperglycaemia) was 2.0% compared to 1.6% with placebo. Hyperglycaemia is also reported as a very rare (<0.01%) spontaneous event.

Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Risperidone

The EU Pharmacovigilance Party of the CPMP has proposed similar wording to that for Seroquel mentioned above.

The current UK label makes no mention of diabetes or hyperglycaemia for risperidone.

Ziprasidone

From the Swedish label:

In a double-blind comparative study, metabolic parameters were measured including weight, fasting insulin, total cholesterol, triglycerides and an insulin resistance (IR) index. Among patients receiving ziprasidone no significant changes from baseline values were observed for any of these metabolic parameters".

Clozapine
From the UK SmPC:
Abnormalities of glucose homeostasis occur uncommonly in approximately 0.35% of CLOZARIL (clozapine) patients in the UK cohort monitored by the CLOZARIL Patient Monitoring Service. Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL (clozapine) treatment in patients with no prior history of hyperglycaemia. Blood glucose levels normalised in most patients after discontinuation of CLOZARIL (clozapine), and a rechallenge in a few cases produced a recurrence of hyperglycaemia. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL (clozapine) particularly if symptoms of polydipsia, polyuria, and weakness develop. With prolonged treatment considerable weight gain has been observed in some patients and further investigation is periodically needed to ensure hyperglycaemia is not missed. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL (clozapine) should be considered when active medical management of the hyperglycaemia has failed.

Seroquel safety database analysis

Note: This summary has been adapted from a review of the company database and since adverse event data constantly changes only qualitative conclusions have been presented here.

- Adverse event data from over 3000 patients exposed to Seroquel during clinical trials has shown that the incidence of adverse events possibly associated with disturbances in glucose regulation is low, and does not increase as duration of exposure to Seroquel increases. No cases of diabetic ketoacidosis or hyperosmolar coma were reported, and a very small number of cases of diabetes mellitus were reported (all of which were considered by the investigator to be unrelated to trial treatment).

- Random plasma glucose data from clinical trials has shown that hyperglycemia (random glucose value $\geq$ 200 mg/dl) was observed in a small number of patients treated with Seroquel, but was not sustained, extreme, or associated with any symptoms. Further, the incidence of hyperglycemia did not increase as the duration of exposure to Seroquel increased. In addition, there were no statistically significant differences between Seroquel and placebo in the mean changes from baseline to endpoint in random plasma glucose levels.

- All the reports received from Japan are either confounded, or have alternative explanations or a negative dechallenge, or had documentation of hyperglycaemia or poor diabetes control prior to receiving Seroquel. These reports provide insufficient information to establish a causal relationship between Seroquel and diabetes, hyperglycaemia, exacerbation of diabetes, or diabetic ketoacidosis.

- Worldwide (including Japan) postmarketing reports comprise cases of new-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, diabetic ketoacidosis or hyperglycaemia. However, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. This position is supported by the literature where the incidence of diabetes mellitus in the schizophrenic population is noted to exceed that in the general population, even prior to the introduction of atypical antipsychotic medications (Dixon L et al 2000; Schiz Bull.26 (4):903-912).

Company position

Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.

There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes.

There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.

EXHIBIT 31

PERGAMON

PNEC

Psychoneuroendocrinology 28 (2003) 83–96

www.elsevier.com/locate/psyneuen

A review of the effect of atypical antipsychotics on weight

H. Nasrallah *

Department of Psychiatry, University of Cincinnati Medical Center, 231 Albert Sabin Way, P.O. Box 670559, Cincinnati, OH 45267-0559, USA

Abstract

Controlled research trials have shown that atypical antipsychotics have important advantages over standard antipsychotics, including a broader spectrum of efficacy and improved tolerability profile, particularly with regard to neurological adverse events such as extrapyramidal symptoms (EPS). Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and other adverse health effects. The mechanisms involved in antipsychotic drug-related weight gain are as yet uncertain, although serotoninergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity.

Keywords: Atypical antipsychotics; Schizophrenia; Weight gain; Long-term therapy

* Tel.: +1-513-558-4615; fax: +1-513-558-4616.
E-mail address: HNasra2905@aol.com (H. Nasrallah).

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Contents

1. Introduction

Atypical antipsychotics are an important advance in the treatment of schizophrenia and other psychoses, and have become widely used as first-line pharmacotherapy for psychosis. One of the main advantages of the atypical antipsychotics over standard antipsychotics is their broad spectrum of efficacy. Unlike the older conventional antipsychotics, atypical antipsychotics are effective in the treatment of all schizophrenia domains (positive, negative, affective, and cognitive symptoms) (Javitt, 1999; Purdon et al., 2001). Conventional antipsychotics (e.g. haloperidol, chlorpromazine) do not always fully resolve positive symptoms, have little effect on negative symptoms, and may worsen cognitive symptoms in some patients (Spohn and Strauss, 1989; Purdon et al., 2001).

As with all drugs, efficacy must be accompanied by a tolerable side-effect profile to optimize clinical effectiveness. Extrapyramidal symptoms (EPS) are a major problem with conventional antipsychotics and often lead to poor compliance (Tran et al., 1997; Davies et al., 1998). Atypical antipsychotics, however, have been shown to cause less EPS than standard antipsychotics, although dose-related EPS do occur with some agents (Owens, 1994; Peuskens, 1995; Daniel et al., 1999). With the declining use of conventional antipsychotics and reduced incidence of acute EPS as well as tardive dyskinesia, other side effects of antipsychotics, such as weight gain, have become more prominent as impediments to clinical effectiveness.

Weight gain is associated with many conventional and some atypical antipsychotics (Allison et al., 1999a) and its degree is dependent on the drug and the individual patient. Weight gain occurs shortly after starting treatment but may plateau or

even decrease after 1 year. Weight gain is linked to a decreased metabolic rate, increased calorie intake, and decreased physical activity (Weinsier et al., 1998; Baptista, 1999), although it is not yet known by which precise mechanisms it is induced by atypical antipsychotics.

The consequences of excessive weight gain (obesity) associated with antipsychotic drugs are likely to include poor compliance or even discontinuation of therapy by the patients. Poor adherence almost always leads to relapse and a worsened long-term outcome (Bernstein, 1987; Fenton et al., 1997). As obesity is frequently a comorbid condition with schizophrenia (Allison et al., 1999b), schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type II diabetes (Mukherjee et al., 1996; Nasrallah, 2000). Particular consideration should therefore be given to the choice of antipsychotic drugs in this patient population with regard to weight change as a potential serious adverse health effect.

This review examines the limited evidence regarding the mechanism of weight gain with antipsychotic drugs and then focuses on the differential effects of atypical antipsychotics on weight. In the majority of the studies discussed, weight gain was assessed for each patient by calculating the difference between body mass index (BMI) at the start and end of treatment. BMI describes relative weight for height and is a widely accepted measure of weight change and classification (WHO, 1998). It is calculated as the weight in kilograms divided by the square of the height in meters. Optimal BMI is between 20 and 25, while 25–30 is regarded as 'overweight' and >30 as 'obese'.

2. Mechanisms of weight gain with atypical antipsychotics

It is generally believed that there are multiple mechanisms by which antipsychotic drugs induce weight gain but their precise nature remains unknown. Weight gain as a drug effect may be a multifactorial process, involving serotonergic, histaminergic, and/or adrenergic neurotransmission (Baptista, 1999). Atypical antipsychotics achieve their therapeutic effects by modulating the activity of these neural pathways. Weight gain as a side effect may be due to the blockade of certain receptors, e.g. 5-HT_{2c}, that modulate appetite and body weight (Stanton, 1995). The ratios between various receptor affinities may also be important. As the atypical antipsychotics vary in their receptor affinity profiles, it would be expected that they differ in their tendency to cause weight gain.

The specific interaction between antipsychotic drugs and hormones (such as insulin and leptin) that regulate appetite and obesity has yet to be fully elucidated. Melkersson et al. (2000) found that olanzapine therapy was associated with increased levels of insulin and leptin, as well as with weight gain. Leptin regulates food uptake and energy expenditure; it is synthesized by fat cells and its serum levels correlate positively with BMI (Kraus et al., 1999). An increase in serum leptin levels has been associated with olanzapine and clozapine therapy (Brömel et al., 1998; Kraus et al., 1999). This increase may be a direct effect of the antipsychotics on the feedback

mechanism for this hormone or an effect of the increased appetite, impaired satiety, and weight gain associated with the antipsychotic drugs.

3. Clozapine

Clozapine is associated with some of the largest weight gains seen with any antipsychotic drug (Stanton, 1995; Sussman and Ginsberg, 1999). Cohen et al. (1990) reported a mean weight gain of 11.2 kg for six patients taking clozapine at maximum doses of 175–600 mg/day for a mean duration of 6.5 months. Included in this group was one patient who had substantial weight gain of 31.3 kg while taking clozapine at a maximum dose of 400 mg/day for 9 months. It should be noted that a gain of >7% of the ideal body weight is considered a health risk. This amounts to about 4 kg for an average woman and 6 kg for an average man.

Leadbetter et al. (1992) reported a mean weight gain of 6.3 kg (9% increase in body weight) in 21 patients over 16 weeks of treatment. Eight (38%) patients experienced marked weight gains (>10% of their body weight). Lamberti et al. (1992) reported a mean weight gain of 7.7 kg for 36 patients receiving a mean clozapine dose of 380 mg/day over 6 months. This increase represented 11% of the patients' maximum ideal weight. Twenty-seven (75%) of the patients gained at least 4.5 kg and 15 (42%) patients gained at least 9 kg.

In a retrospective study of 82 patients treated with clozapine 500–600 mg/day for up to 90 months, Umbricht et al. (1994) found that about 50% of patients became substantially overweight (≥20%). Patients who were underweight at baseline had significantly higher percentage weight increases than those with ideal weight and those who were overweight. The cumulative incidence rates were >80% of patients for a 10% weight gain and 38% of patients for a 20% weight gain. Weight gain occurred mostly within the first year but continued into the third year.

Frankenburg et al. (1998) found significant mean increases (5.9 and 3.3 kg/m^2 in female and male patients, respectively) in BMI among 42 patients receiving clozapine over a 3-year period. The final BMI appeared to be dependent on the baseline BMI and the dose of clozapine.

Finally Reinstein et al. (1999) reported significant weight loss (mean 4.2 kg; range 0.45–18.6 kg over 10 months) with the addition of quetiapine to the treatment regimen of 65 patients who had previously been on clozapine monotherapy. Furthermore, they reported a significant improvement in glycemic control in three (20%) of 13 patients who developed diabetes during clozapine monotherapy.

4. Olanzapine

Olanzapine is associated with significant weight gain with a magnitude comparable to that produced by clozapine (Jibson and Tandon, 1998). Nemeroff (1997) reviewed the safety and efficacy data from four clinical trials in which olanzapine was compared with placebo and/or haloperidol in nearly 3000 patients. Olanzapine patients

had a dose-related increase in weight, achieving after 1 year a mean weight gain of approximately 12 kg with a high dose (12.5–17.5 mg/day), compared with a mean weight gain of 3 kg with a low dose (1 mg/day) (Fig. 1) (Nemeroff, 1997). Weight gain was greatest for patients who had a starting dose of 12.5–17.5 mg/day of olanzapine and/or were underweight (as indicated by BMI) at the start of the study.

Beasley (1997) reported that 41% of a total of 1455 patients receiving olanzapine in four combined studies experienced a clinically significant (≥7%) weight gain. The incidence of weight gain was highest (32%) among patients who were underweight at baseline and lowest (11%) among those who were overweight. Most weight gain occurred during the first 6–8 weeks of therapy and reached a plateau by the end of the first year. Further evidence of olanzapine-associated weight gain provided by Weiden et al. (1996) showed that after >6 weeks of olanzapine treatment, one-third of the patients reported weight gain as the 'most problematic' side effect. Weight gain occurred in most of the 15 patients and was regarded as a serious problem for 3/15 (20%) patients.

In addition, a study of nine patients with schizophrenia showed that 16 months of treatment with olanzapine was associated with a rise in triglyceride levels and mean weight gain of 10 kg (Sheitman et al., 1999). The rise in triglyceride levels is an important factor for some patients because of its link with an increased risk for coronary artery disease. Finally, a recent study of olanzapine with or without fluoxetine in treatment-resistant depression reported a weight gain of 6.07 kg with olanzapine alone over 8 weeks (Shelton et al., 2001). It may be that patients with mood disorders are especially susceptible to weight gain with olanzapine.

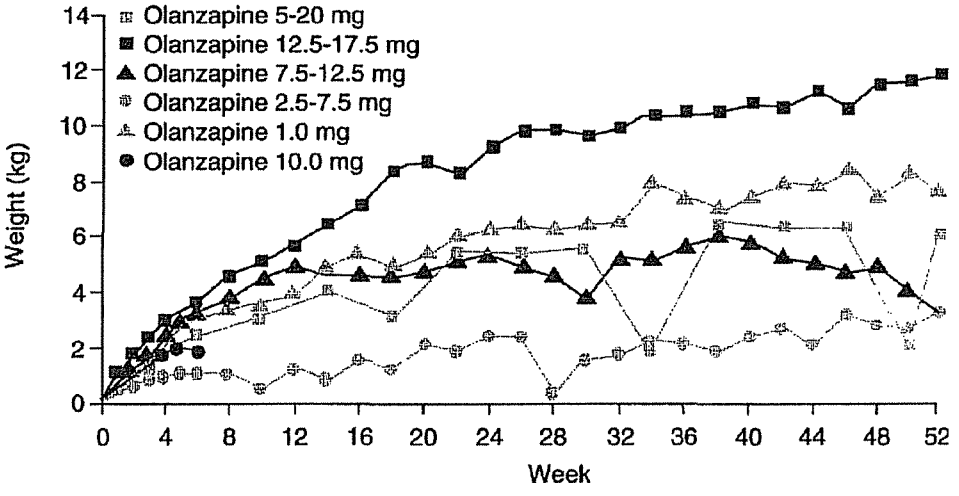


Fig. 1. Mean change in weight over time at different olanzapine dosages. Data from four different studies combined. Olanzapine dosages were as follows: Study 1—fixed at 1 and 10 mg/day; Study 2—flexible within three dose ranges (2.5–7.5, 7.5–12.5, and 12.5–17.5 mg/day); Study 3—as Study 2 with the addition of a fixed dose of 1 mg/day; and Study 4—flexible within the range 5–20 mg/day. Adapted from Nemeroff (1997). Copyright 1997, Physicians Postgraduate Press. Reprinted by permission.

5. Risperidone

Risperidone is associated with modest weight gain that is not dose related. The literature reveals consistent values for weight gain with risperidone therapy. Claus et al. (1992) reported a mean weight gain of 2 kg after 12 weeks of treatment with risperidone at a mean final dose of 12 mg/day. Owens (1994) reported mean weight gains of 1–2 kg after 8 weeks of treatment with risperidone at 2–16 mg/day.

A mean weight gain of 2.8 kg occurred after 8 weeks of treatment in 11 patients randomized to 2, 6, 10, or 16 mg/day risperidone. The change in weight from baseline was statistically significant, as was the difference in weight change between the risperidone and placebo groups. There was no significant correlation between weight gain and risperidone dose or plasma concentration (Anderson et al., 1993). Brecher and Geller (1997) reported an average weight gain of 2.6 kg among 1200 patients treated for a mean duration of 213 days (30 weeks) in long-term risperidone trials.

A recent study comparing risperidone and haloperidol over 1 year showed a mean weight gain of 2.3 kg in the risperidone group and a decrease of 0.73 kg in the haloperidol group (Csernansky et al., 2002).

6. Ziprasidone

Ziprasidone has been associated with minimal weight loss, minimal weight gain, or no effect on weight. A pooled analysis of four short-term (4–6 week) studies showed the proportion of patients who experienced weight gain exceeding 7% body weight was significantly greater in those treated with ziprasidone (dose range 10–200 mg/day) compared with placebo (10 versus 4%) (Geodon (ziprasidone HCl) Prescribing Information, 2001). The same analysis indicated that the overall incidence of anorexia adverse events with ziprasidone was low (2 versus 1% placebo) but was reported to be dose related.

In a randomized, placebo-controlled, double-blind study, Arato et al. (1999) assessed ziprasidone in 219 chronic schizophrenia patients for 1 year, at three dose levels (40, 80, and 160 mg/day). Patients in this study were carefully monitored, being either in hospital or in sheltered accommodation with continuous medical or nursing supervision. Ziprasidone was not associated with weight gain but it remains to be established whether these results will replicate in patients managed in an unsupervised outpatient setting.

In a head-to-head, double-blind, 6-week, randomized trial, ziprasidone was associated with a small increase in weight (n = 116, 0.93 kg, 0.24 kg/m^2) that was significantly lower than with olanzapine (n = 120, 3.57 kg, 1.17 kg/m^2) (Simpson et al., 2001). However, the incidence of gastrointestinal-related adverse events such as dyspepsia (11.8 versus 7.5%) and nausea (10.3 versus 6.0%) was higher amongst patients receiving ziprasidone than those receiving olanzapine and the extent to which this may have affected food intake and weight change is not known.

Results from various studies of these four atypical antipsychotics (clozapine, olanzapine, risperidone, and ziprasidone) were included in a meta-analysis by Allison et

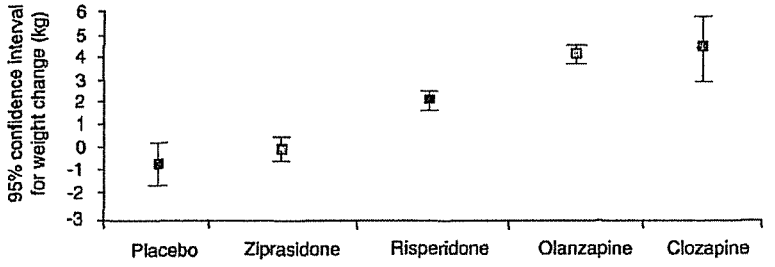


Fig. 2. Mean weight change with 95% confidence intervals after 10 weeks on standard drug doses. Adapted from Allison et al. (1999a). Copyright 1999, American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.

al. (1999a). The mean weight change was estimated after 10 weeks of treatment with antipsychotic drugs at a standard dose (Fig. 2) (Allison et al., 1999a). The results, with substantial weight gain for clozapine and olanzapine, modest weight gain for risperidone, and negligible weight gain for ziprasidone, were consistent with previous reports as described above.

7. Quetiapine

Results from several clinical trials have shown that short-term quetiapine treatment is associated with modest weight gain that is not dose related. The effects on weight are neutral when quetiapine is used as long-term monotherapy.

A total of 2216 patients who had participated in controlled, uncontrolled, and open-label extension trials were included in an analysis of weight change in long-term (12 months) quetiapine treatment (Jones et al., 2000; Rak et al., 2000). Analysis of the overall data showed a small mean weight increase of 2.08 kg (n = 778) over the first 5–6 weeks of treatment (Table 1) and no dose-related weight gain (Table 2). Over longer treatment periods, the increases from baseline showed little change (Table 1) and remained unrelated to dose (Table 2). The mean dose of quetiapine at 9–12 months was 428 mg/day. An analysis of weight change by BMI categories at baseline revealed a trend for greater weight gain in patients with low baseline

Table 1
Mean weight change from baseline in patients treated with quetiapine during controlled, uncontrolled, and open-label extension trials; data from Rak et al. (2000)

Duration of treatment	No. of patients	Mean weight change, kg (+SE)
5–6 weeks	778	2.08 (0.15)
9–10 weeks	171	2.16 (0.46)
6–9 months	556	1.85 (0.48)
9–12 months	360	2.77 (0.56)

Table 2
Mean weight change in patients receiving different quetiapine doses during controlled, uncontrolled, and open-label extension trials; adapted from Jones et al. (2000)

Dose (mg)	Mean weight change (kg)	
	5–6 weeks of treatment	9–12 months of treatment
<125	1.21	1.78
125–225	2.95	1.38
>225–450	2.13	3.83
>450–675	1.95	2.26
>675	2.05	2.13

BMIs (<23) than in patients with normal (23–27) or high (>27) baseline BMIs. Only one patient withdrew from treatment because of weight gain. It should be noted that most of the patients included in this analysis had participated in studies in which antipsychotics other than quetiapine were allowed. It is therefore difficult to attribute weight gain specifically to quetiapine or the other antipsychotics or a combination of both.

The absence of a dose-related weight gain is consistent with the results of an earlier double-blind, dose-ranging study in which 361 patients received quetiapine for up to 6 weeks and in which no apparent relationship was found between weight change and dose (Arvanitis and Miller, 1997; Jones et al., 2000). A separate analysis included patients from controlled, uncontrolled, and open-label extension trials in which quetiapine was the only antipsychotic permitted (Brecher et al., 2000; Brecher and Melvin, 2001). A total of 427 patients received a mean dose of 475 mg/day after 1 year of open-label quetiapine treatment. There was minimal weight gain over an 80-week period (Fig. 3) (Brecher et al., 2000).

Quetiapine had no overall effect on weight across the baseline BMI range. The relationship between weight change and BMI was examined in a subset of 178 patients who had received quetiapine for at least 26 weeks (mean duration of 18.6 months) at a mean final dose of 473 mg/day. Patients were categorized according to their baseline BMIs (<18.5 = underweight; 18.5 to <25 = normal weight; 25 to <30 = overweight; 30 to <35 = obese; and ≥35 = severely obese). Small numbers of patients in some of these categories resulted in wide 95% confidence intervals associated with the mean weight change from baseline. Fig. 4 shows that the 95% confidence intervals of the mean weight change from baseline included zero when all BMI groups were considered together and individually (with the exception of the severely obese) (Brecher et al., 2000). These results indicate an absence of weight effect across the BMI range with long-term quetiapine treatment except in severely obese patients, where quetiapine was associated with a statistically significant decrease in weight. The effect of quetiapine was not related to dose or gender. Fig. 5 shows weight changes by dose group, using the modal dose value for the last recorded weight (endpoint) value (Brecher et al., 2000). There were no statistically significant changes from baseline in mean weight. The 95% confidence intervals of

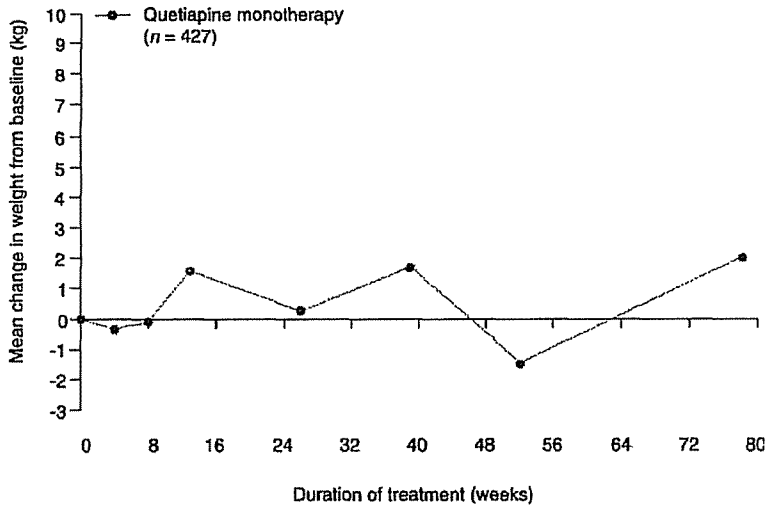


Fig. 3. Mean weight change from baseline during quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

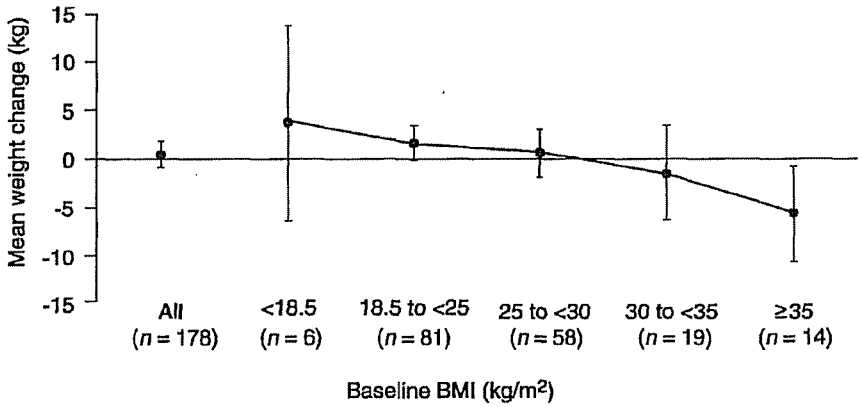
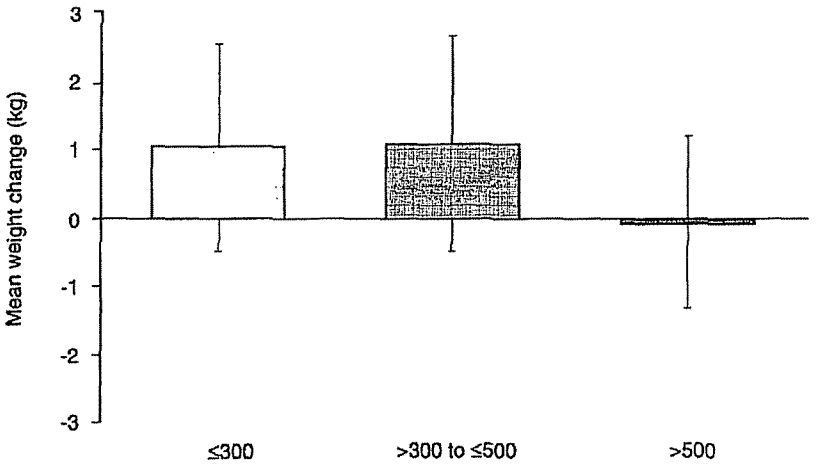


Fig. 4. Mean weight change with 95% confidence intervals from baseline to endpoint by baseline category in patients receiving quetiapine monotherapy for at least 6 months. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

the mean weight change from baseline included zero for all three dose groups, indicating that the effect of quetiapine on patient weight was neutral across the dose range. There was also no correlation between increasing dose and mean long-term weight changes.

These studies cumulatively suggest that quetipine is associated with only minimal weight changes during short-term use which are not dose related and do not increase over time. Further, given the chronic nature of maintenance antipsychotic therapy, the long-term effect of quetiapine on weight change appears to be neutral overall and potentially weight normalizing in some obese patients.



Mean duration of treatment (days)	343	407	327
No. patients	103	94	174

Fig. 5. Mean weight change with 95% confidence intervals from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

8. Discussion

Weight gain can be a serious iatrogenic health problem in patients with schizophrenia and other psychoses. It is an important side effect of antipsychotic medication and may have adverse implications for adherence with long-term antipsychotic therapy. Excessive weight gain may also lead to other adverse health effects, e.g. type II diabetes, hyperlipidemia, and cardiovascular disease. Weight gain occurs to varying extents depending on the drug.

In the atypical class of antipsychotics, clozapine and olanzapine are associated with the most significant weight gain. Risperidone is associated with modest weight changes that are not dose related. Ziprasidone has a relatively low risk of weight gain during short-term treatment and no overall weight gain during long-term treatment in patients under continuous clinical supervision.

Quetiapine is associated with modest short-term weight changes that do not increase over time and are not dose related. The overall effect of quetiapine on weight in long-term treatment is neutral, with some weight loss in severely obese patients. Quetiapine has favorable efficacy and tolerability profiles, which have resulted in high levels of patient satisfaction and the normalization of eating habits

in 73% of the study population (Hellewell et al., 1999). Hence, the available data suggest that quetiapine has a favorable benefit:risk profile. Taking into account both the minimal weight change and placebo-level EPS across the full dose range, quetiapine should be considered as a first-choice antipsychotic in the long-term treatment of schizophrenia.

While high BMI and obesity are well-known risk factors for diabetes and are associated with insulin resistance, more recently some of the atypical antipsychotics have themselves been linked to impaired glucose metabolism and diabetes mellitus (see supplement Sussman, 2001, for review of this area). Because patients with psychosis (schizophrenia and mania) have an increased risk for comorbid diabetes even before antipsychotic pharmacotherapy is initiated (Mukherjee et al., 1996; Cassidy et al., 1999), it can be difficult to determine a causal link between atypical antipsychotic-induced diabetes, antipsychotic exacerbation of pre-existing diabetes, or the development of diabetes as a comorbidity of the psychotic disorder itself. However, while there have been no definitive well-controlled and randomized trials, there is some evidence from case reports in the literature that clozapine (Koval et al., 1994; Popli et al., 1997) and olanzapine (Wirshing et al., 1999; Goldstein et al., 1999) may impair glucose metabolism and increase the risk of diabetes in patients with schizophrenia (Henderson, 2002). Interestingly in another recent study, Newcomer et al. (2002) found that glucose levels were significantly elevated in nondiabetic schizophrenia patients treated with clozapine and olanzapine but not in those treated with risperidone or typical agents.

In conclusion, the differential weight gain of various atypicals should be considered in the selection of a first-line antipsychotic, given the potentially serious health effects of obesity. However, other adverse events such as dose-dependent EPS (Jibson and Tandon, 1998), hyperprolactinemia-induced sexual dysfunction (Turrone et al., 2002), and cardiac conduction effects (Glassman and Bigger, 2001) should also be taken into consideration in the selection of a first-line atypical antipsychotic. By minimizing adverse effects, patient adherence to long-term treatment of psychotic disorders is substantially increased.

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EXHIBIT 32

Weight and Diabetes Sell Sheet VM 08 15 05 v6

Hello, this is Christine Ney, Scientific Alignment Manager for Seroquel I want to follow-up with you on the Weight and Diabetes Sell Sheet you received recently This selling tool contains data on both weight gain and diabetes that you'll find helpful as you engage customers about SEROQUEL's tolerability -- and address their comments and questions on these issues

First, you'll notice that key data and summary statements (even footnotes!) are presented clearly in this compact, two-sided format Then, you'll notice the message points that help you focus and organize your thoughts with facts like

- Overall weight gain for SEROQUEL-treated patients diagnosed with schizophrenia was 2 3 kg after at least 26 weeks of treatment

You can also point out that

- In monotherapy bipolar mania trials, the average weight gain was 1 8 kg In adjunct therapy bipolar mania trials, the average gain was 1 97 kg

And

- In pivotal trials (of 3- to 12-week duration), with "weight gain" defined as an increase of 7% or more from baseline, the incidence was 13% to 23% in patients receiving SEROQUEL, versus 4% to 7% in patients on placebo

- There were no discontinuations due to weight gain with SEROQUEL in pivotal trials for schizophrenia and bipolar mania

For Diabetes consider pointing out that

- Seroquel has over 8 million patient exposures worldwide since it was approved for use in 1997 While hyperglycemia-related adverse events have been reported in patients taking atypical antipsychotics, including SEROQUEL, to date the available data has not established a causal link between diabetes and SEROQUEL

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL

Our objective is to neutralize customer objections to SEROQUEL's weight and diabetes profile This is possible with messages that are supported by data -- the kind of message you can take away from the Weight and Diabetes Sell Sheet

I think you'll appreciate the potential of this tool Then, don't forget to refocus the call on SEROQUEL's Trusted Tolerability profile, highlighting the low incidence of Akathisia and EPS with SEROQUEL

Thanks everyone and good selling!

EXHIBIT 34

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

James L. Gaskill, PharmD
Director
Promotional Regulatory Affairs
AstraZeneca
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Mailstop D1C-715
Wilmington, DE 19803-8355
Fax (302) 886-2822

RE: NDA # 20-639
Seroquel® (quetiapine fumarate) Tablets
MACMIS ID # 14670

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (238110) for Seroquel® (quetiapine fumarate) tablets (Seroquel) submitted by AstraZeneca under cover of Form FDA 2253. This piece is false or misleading because it minimizes the risk of hyperglycemia and diabetes mellitus and fails to communicate important information regarding neuroleptic malignant syndrome, tardive dyskinesia, and the bolded cataracts precaution. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i). The promotional material raises significant public health and safety concerns through its minimization of the risks associated with Seroquel.

Background

According to its FDA-approved product labeling (PI), Seroquel is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex and for the treatment of schizophrenia.

The PI includes important warnings and precautions. It states (in pertinent part):

WARNINGS

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical

manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing

a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

Orthostatic Hypotension
SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. SEROQUEL should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

Cataracts
Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures
As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

* * *

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, FDA asked all manufacturers of atypical antipsychotics to include a warning in their PI regarding this risk on September 11, 2003. FDA believes that the safe use of Seroquel can be enhanced by informing prescribers and patients about these events and increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment and thus reduce the risk for the most serious outcomes. The PI including the hyperglycemia and diabetes mellitus warning for Seroquel was approved on January 12, 2004.

Misleading Presentation

Page two of the professional sales aid starts with a prominent header, which states "Diabetes Information," and then presents the following five bullets:

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

The first two bullets contain information from the Warning in Seroquel's PI regarding Hyperglycemia and Diabetes Mellitus concerning the observed hyperglycemic events and the areas of uncertainty about the glucose abnormality findings. While the agency acknowledges that it has not been established whether Seroquel causes diabetes, you fail to include information regarding the increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. The increased risk may be due to confounding factors and is not completely understood, but a warning about it was recently added to Seroquel's PI to enhance the safe use of Seroquel and protect public health. Because your bullets about the relationship between the use of Seroquel and hyperglycemia leave out this information, the bullets are misleading and undermine the warning.

Furthermore, the fourth bullet claims that the percentage of diabetes or diabetes-related events in post-marketing reports is "very rare (<0.01%) with Seroquel." In light of the voluntary nature of post-marketing adverse event reporting by healthcare professionals and patients, it is infeasible to obtain an accurate percentage of all diabetes or diabetes-related

adverse events associated with Seroquel based upon these reports. Therefore, quantifying post-marketing adverse events in this manner is misleading.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the professional sales aid fails to include relevant risk information about the Warnings and Precautions that it presents. While the professional sales aid states that "Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia," it fails to reveal that the risk of developing the condition and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered increase. The sales aid also fails to mention that the syndrome may partially or completely remit if antipsychotic treatment is withdrawn. Additionally, the professional sales aid states that "A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL." This statement is misleading in that it fails to reveal that NMS is a potentially fatal symptom complex associated with the administration of Seroquel. Furthermore, the professional sales aid fails to convey the important information from the PI regarding the clinical manifestations of NMS and that management of NMS should include immediate discontinuation of antipsychotic drugs.

The professional sales aid states that "Precautions include the risk of seizures, orthostatic hypotension, and cataract development." This statement is misleading because it omits material facts from the PI about these risks. In particular, it fails to mention important information from the bolded cataracts precaution recommending that physicians examine all patients at initiation of Seroquel treatment or shortly thereafter, and at six month intervals during chronic treatment, to detect cataract formation.

Conclusion and Requested Action

For the reasons discussed above, the professional sales aid misbrands Seroquel in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i).

DDMAC requests that AstraZeneca immediately cease the dissemination of violative promotional materials for Seroquel such as those described above. Please submit a written response to this letter on or before November 30, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Seroquel the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14670 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seroquel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Dean
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EXHIBIT 35

Nolvadex—Cont.

NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3–5 days of beginning NOLVADEX and cleared within 2–5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20–40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the EBCTCG 1990 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for two years or longer than in those that used tamoxifen for less than two years. There was no indication that doses greater than 20 mg per day were more effective. In B-14, the NSABP adjuvant study in women with node-negative breast cancer, one 10 mg NOLVADEX tablet was given twice a day for at least five years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see CLINICAL PHARMACOLOGY). The optimal duration of adjuvant NOLVADEX therapy remains to be determined.

HOW SUPPLIED

10 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. NDC 0310-0600.

20 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets. NDC 0310-0604.

Store at controlled room temperature, 20–25° C (68–77° F) [see USP]. Dispense in a well-closed, light-resistant container.

ZENECA Pharmaceuticals
A Business Unit of ZENECA Inc.
Wilmington, DE 19850-5437 USA
SIC 64130-00 Rev S 02/98

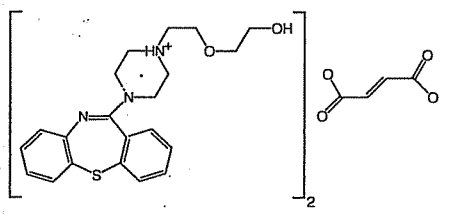
Shown in Product Identification Guide, page 346

SEROQUEL® ℞

[serō-quĕl]
(quetiapine fumarate)
tablets

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo*[b,f]*[1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2{\cdot}C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow) and 200 mg (white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain; serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}= 1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL. SEROQUEL'S antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL'S antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro,* quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose and was recovered in the urine and feces, respectively. Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10–30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed. (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6, and 3A4.

Quetiapine oral clearance is induced by the prototype cytochrome P450 3A4 inducer, phenytoin. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin (See **DRUG INTERACTIONS** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium, or lorazepam. (See **DRUG INTERACTIONS** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the management of the manifestations of psychotic disorders was established in 3 short-term (6-week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600, and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score, with the maximum effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose of SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS. Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of SEROQUEL was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects

)QUEL for extended periods should periodically
:he long-term usefulness of the drug for the in-
ıtient (See **DOSAGE AND ADMINISTRA-**

NDICATIONS

L is contraindicated in individuals with a known
ivity to this medication or any of its ingredients.

:S

: Malignant Syndrome (NMS)

ly fatal symptom complex sometimes referred to
ptic Malignant Syndrome (NMS) has been re-
ıssociation with administration of antipsychotic
possible cases of NMS [2/2387 (0.1%)] have been
ı clinical trials with SEROQUEL. Clinical mani-
of NMS are hyperpyrexia, muscle rigidity, altered
tus, and evidence of autonomic instability (irreg-
or blood pressure, tachycardia, diaphoresis, and
srhythmia). Additional signs may include ele-
tinine phosphokinase, myoglobinuria (rhabdomy-
d acute renal failure.

ostic evaluation of patients with this syndrome is
d. In arriving at a diagnosis, it is important to
ses where the clinical presentation includes both
edical illness (e.g., pneumonia, systemic infection,
ıntreated or inadequately treated extrapyramidal
symptoms (EPS). Other important considerations
erential diagnosis include central anticholinergic
eat stroke, drug fever, and primary central ner-
em (CNS) pathology.

ıgement of NMS should include: 1) immediate dis-
ion of antipsychotic drugs and other drugs not es-
ı concurrent therapy; 2) intensive symptomatic
: and medical monitoring; and 3) treatment of any
ant serious medical problems for which specific
ts are available. There is no general agreement
ecific pharmacological treatment regimens for

nt requires antipsychotic drug treatment after re-
ım NMS, the potential reintroduction of drug ther-
ld be carefully considered. The patient should be
monitored since recurrences of NMS have been re-

)yskinesia

ıme of potentially irreversible, involuntary, dyski-
vements may develop in patients treated with an-
ic drugs. Although the prevalence of the syndrome
to be highest among the elderly, especially elderly
it is impossible to rely upon prevalence estimates to
at the inception of antipsychotic treatment, which
are likely to develop the syndrome. Whether anti-
c drug products differ in their potential to cause tar-
kinesia is unknown.

of developing tradive dyskinesia and the likelihood
will become irreversible are believed to increase as
ıtion of treatment and the total cumulative dose of
:hotic drugs administered to the patient increase.
r, the syndrome can develop, although much less
ıly, after relatively brief treatment periods at low

s no known treatment for established cases of tar-
skinesia, although the syndrome may remit, par-
r completely, if antipsychotic treatment is with-
Antipsychotic treatment, itself, however, may sup-
r partially suppress) the signs and symptoms of the
ne and thereby may possibly mask the underlying
. The effect that symptomatic suppression has upon
g-term course of the syndrome is unknown.

these considerations, SEROQUEL should be pre-
in a manner that is most likely to minimize the oc-
:e of tardive dyskinesia. Chronic antipsychotic treat-
hould generally be reserved for patients who appear
r from a chronic illness that (1) is known to respond
ipsychotic drugs, and (2) for whom alternative,
effective, but potentially less harmful treatments
available or appropriate. In patients who do require
treatment, the smallest dose and the shortest dura-
treatment producing a satisfactory clinical response
be sought. The need for continued treatment should
ssessed periodically.

s and symptoms of tardive dyskinesia appear in a pa-
n SEROQUEL, drug discontinuation should be con-
d. However, some patients may require treatment
EROQUEL despite the presence of the syndrome.

!AUTIONS

al

static Hypotension: SEROQUEL may induce ortho-
hypotension associated with dizziness, tachycardia
ı some patients, syncope, especially during the initial
itration period, probably reflecting its α_1-adrenergic
onist properties. Syncope was reported in 1% (22/
of the patients treated with SEROQUEL, compared
)% (0/206) on placebo and about 0.5% (2/420) on active
)l drugs. The risk of orthostatic hypotension and syn-
nay be minimized by limiting the initial dose to 25 mg
ee **DOSAGE AND ADMINISTRATION**). If hypoten-
sion occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to defect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range that was apparent early on during treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, but about 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient, and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to prestudy levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal and Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3–5 day period of initial dose titration, and also at times of reinitiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3–5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a noninducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Continued on next page

Seroquel—Cont.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Although data are not available from clinical studies, caution is indicated when SEROQUEL is administered with a potent enzyme inhibitor of cytochrome P450 3A (e.g., ketoconazole, itraconzaole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs:

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (one a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/kg) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the result of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women, and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients. (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time of worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% of SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded in the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

[See table 1 at bottom of next page]

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness of EPS associated with SEROQUEL treatment. Three methods were used to measure EPS (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapydramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

[See table at bottom of next page]

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS, and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinical important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- 6-week-placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

dverse Events Observed During the Premarketing on of SEROQUEL

ıg is a list of COSTART terms that reflect treatıergent adverse events as defined in the introducıe ADVERSE REACTIONS section reported by paeated with SEROQUEL at multiple doses ≥ 75 mg/ ing any phase of a trial within the premarketing ıe of approximately 2200 patients. All reported ıre included except those already listed in Table 1 or re in labeling, those events for which a drug cause ıote, and those event terms which were so general as ıinformative. It is important to emphasize that, althe events reported occurred during treatment with UEL, they were not necessarily caused by it.

are further categorized by body system and listed in f decreasing frequency according to the following ons: frequent adverse events are those occurring in ; 1/100 patients (only those not already listed in the ed results from placebo-controlled trials appear in ting); infrequent adverse events are those occurring 0 to 1/1000 patients; rare events are those occurring r than 1/1000 patients.

ıs System: ***Frequent:*** hypertonia, dysarthria; ***Infre-*** abnormal dreams, dyskinesia, thinking abnormal, dyskinesia, vertigo, involuntary movements, confumnesia, psychosis, hallucinations, hyperkinesia, licreased* urinary retention, incoordination, paranoid n, abnormal gait, myoclonus, delusions, manic reacpathy, ataxia, depersonalization, stupor, bruxism, cat- reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal me, choreoathetosis, delirium, emotional lability, eu-, libido decreased*, neuralgia, stuttering, subdural oma.

as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** ain, pelvic pain*, suicide attempt, malaise, photosen- reaction, chills face edema, moniliasis; ***Rare:*** abdonlarged.

tive System: ***Frequent:*** anorexia; ***Infrequent:*** ıd salivation, increased appetite, gamma glutamyl ıeptidase increased, gingivitis, dysphagia, flatulence, ıenteritis, gastritis, hemorrhoids, stomatitis, thirst, caries, fecal incontinence, gastroesophageal reflux, ıemorrhage, mouth ulceration, rectal hemorrhage, e edema; ***Rare:*** glossitis, hematemesis, intestinal obion, melena, pancreatitis.

ovascular System: ***Frequent:*** palitation; ***Infrequent:*** ilatation, QT interval prolonged, migraine, bradycarerebral ischemia, irregular pulse, T wave abnormality, ıe branch block, cerebrovascular accidenct, deep ıbophlebitis, T wave inversion; ***Rare:*** angina pectoris, fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL® (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25–50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1–2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25–50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400–500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, in patients with hepatic impairment, and in patients who are debilitated or who had a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital. (See Drug Interactions under **PRECAUTIONS**)

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required, and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to SEROQUEL.

Continued on next page

Table 1. Treatment-Emergent Adverse Experience
Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

System/ rred Term	SEROQUEL (n=510)	Placebo (n=206)
as a Whole		
.dache	19%	18%
ıenia	4%	3%
.ominal pain	3%	1%
k pain	2%	1%
er	2%	1%
ous System		
ınolence	18%	11%
ziness	10%	4%
stive System		
ıstipation	9%	5%
Mouth	7%	3%
;pepsia	6%	2%
liovascular System		
;tural hypotension	7%	2%
:hycardia	7%	5%
abolic and Nutritional Disorders		
ight gain	2%	0%
ı and Appendages		
sh	4%	3%
ɔiratory System		
initis	3%	1%
cial Senses		
r pain	1%	0%

vents for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the llowing: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, ıyalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, ry skin, amblyopia, and urinary tract infection.

e Groups	Placebo	SEROQUEL 75 mg	150 mg	300 mg	600 mg	750 mg
kinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
S incidence	16%	6%	6%	4%	8%	6%
icholinergic edications	14%	11%	10%	8%	12%	11%

Seroquel—Cont.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
Store at 25°C (77°F) excursions permitted to 15–30°C (59–86°F). [See USP]

ANIMAL TOXICOLOGY

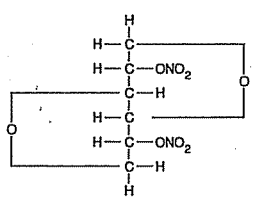
Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10–250 mg/kg in rats, 75–750 mg/kg in mice; these doses are 0.1–3.0, and 0.1–4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.
In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.
Manufactured by:
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5347
64122-00 Rev C 11/97
Shown in Product Identification Guide, page 346

SORBITRATE®

[*sorb 'i-trate*]
(Isosorbide Dinitrate)

DESCRIPTION

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins.
Isosorbide dinitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of 70°C and has an optical rotation of +134° (c = 1.0, alcohol, 20°C). Isosorbide dinitrate is freely soluble in organic solvents such as acetone, alcohol, and ether; but is only sparingly soluble in water.
SORBITRATE is available as:

SORBITRATE® CHEWABLE TABLETS USP
5 mg Chewable Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, confectioner's sugar, corn starch, flavor, hydrogenated vegetable oil, magnesium stearate, mannitol, povidone, Yellow 10.
SORBITRATE® ORAL TABLETS USP
5 mg Oral Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
10 mg Oral Tablet. Each tablet contains 10 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
20 mg Oral Tablet. Each tablet contains 20 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
30 mg Oral Tablet. Each tablet contains 30 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
40 mg Oral Tablet. Each tablet contains 40 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.

CLINICAL PHARMACOLOGY

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.
Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.
Pharmacokinetics: Once absorbed, the distribution volume of isosorbide dinitrate is 2–4 L/kg, and this volume is cleared at the rate of 2–4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is effected primarily by denitration to the 2-mononitrate (15%–25%) and the 5-mononitrate (75%–85%).
Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.
The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10–12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (eg, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.
Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had *less* exercise tolerance at the end of the daily dose-free interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.
Bioavailability of ISDN after single sublingual doses is 40%–50%. Multiple-dose studies of sublingual ISDN pharmacokinetics have not been reported; multiple-dose studies of ingested ISDN have observed progressive increases in bioavailability during chronic therapy. Serum levels of ISDN reach their maxima 10–15 minutes after sublingual dosing.
Absorption of isosorbide dinitrate after oral dosing is nearly complete, but bioavailability is highly varible (10%–90%), with extensive first-pass metabolism in the liver. Serum levels reach their maxima about an hour after ingestion. The average bioavailability of ISDN is about 25%; most studies have observed progressive increases in bioavailability during chronic therapy.
The absorption kinetics of chewable isosorbide dinitrate tablets have not been studied. Absorption of ingested ISDN is known to be nearly complete, although bioavailability is highly variable. Ingested ISDN undergoes extensive first-pass metabolism in the liver; it is not known what portion of this first-pass effect is avoided by buccal absorption of the chewable formulation.
Kinetic studies of absorption of immediate-release formulations of ISDN have found highly variable bioavailability with extensive first-pass metabolism in the liver. Most such studies have observed progressive increases in bioavailability during chronic therapy.
Clinical Trials: In a controlled trial in which 0.4 mg of sublingual nitroglycerin took 1.9 minutes to begin to produce an anti-anginal effect, 5 mg of sublingual ISDN took 3.4 minutes to begin to produce a similar effect. In the same trial, the anti-anginal effect of the sublingual nitrogylcerin was evident for about an hour, while that of the sublingual ISDN lasted about 2 hours.
In other controlled trials, the anti-anginal efficacy of sublingual ISDN has persisted for periods ranging from 30 minutes up to 4 hours.
Multiple-dose trials of sublingual ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using sublingual ISDN is not known.
In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.
Controlled trials of single oral doses of isosorbide dinitrate have demonstrated effective reductions in exercise-related angina for up to 8 hours. Anti-anginal activity is present about 1 hour after dosing.
Most controlled trials of multiple-dose oral ISDN taken every 12 hours (or more frequently) for several weeks have shown statistically significant anti-anginal efficacy for only 2 hours after dosing. Once-daily regimens, and regimens with at least one daily interval of at least 14 hours (eg, a regimen providing doses at 0800, 1400 and 1800) have shown efficacy after the first dose of each day that was similar to that shown in the single-dose studies cited above.
In controlled trials in which sublingual nitroglycerin took $1^1/_2$–2 minutes to begin to produce an anti-anginal effect, chewable ISDN tablets took $2^1/_2$–3 minutes to begin to produce a similar effect. In these same trials, the anti-anginal effect of sublingual nitroglycerin was evident for about 1–$1^1/_2$ hours, while that of chewable ISDN lasted about an hour longer.
Clinical trials of chewable ISDN have used doses of 5 and 10 mg. It is not known whether lower doses would be equally effective.
Multiple-dose trials of chewable ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using chewable ISDN is, because of the rapid onset of action of this formulation, probably somewhat longer.
From large, well-controlled studies of other nitrates, it is reasonable to believe that the maximal achievable daily duration of anti-anginal effect from isosorbide dinitrate is about 12 hours. No dosing regimen for isosorbide dinitrate has, however, ever actually been shown to achieve this duration of effect. In the absence of data from multiple-dose trials, and considering the capacity of organic nitrates to induce tolerance, it is not reasonable to assume that multiple sublingual ISDN tablets taken during the course of a day will all have similar effects.

INDICATIONS AND USAGE

SORBITRATE sublingual tablets and chewable tablets are indicated for the prevention and treatment of angina pectoris due to coronary artery disease. However, because the onset of action of these tablets is significantly slower than that of sublingual nitroglycerin, they are not the drug of first choice for abortion of an acute anginal episode.
SORBITRATE oral tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of immediate release oral isosorbide dinitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide dinitrate is contraindicated in patients who are allergic to it or other nitrates.

WARNINGS

The benefits of isosorbide dinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitor-

must be used to avoid the hazards of hypotension and ıycardia. Because the effects of oral and chewable ISDN ıets are so difficult to terminate rapidly, this formulation ot recommended in these settings.

ECAUTIONS

ıeral: Severe hypotension, particularly with upright ture, may occur with even small doses of isosorbide dini- te. This drug should therefore be used with caution in ients who may be volume depleted or who, for whatever son (eg, diuretics), are already hypotensive. Hypotension uced by isosorbide dinitrate may be accompanied by par- ıxical bradycardia and increased angina pectoris.

rate therapy may aggravate the angina caused by hyper- phic cardiomyopathy.

tolerance to isosorbide dinitrate develops, the effect of ɔlingual nitroglycerin on exercise tolerance, allthough ll observable, is somewhat blunted.

industrial workers who have had long-term exposure to known (presumably high) doses of organic nitrates, toler- ce clearly occurs. Chest pain, acute myocardial infarction, d even sudden death have occurred during temporary thdrawal of nitrates from these workers, demonstrating e existence of true physical dependence.

me clinical trials in angina patients have provided nitro- rcerin for about 12 continuous hours of every 24-hour day. uring the daily dose-free intervals in some of these trials, ginal attacks have been more easily provoked than before eatment, and patients have demonstrated hemodynamic bound and decreased exercise tolerance. The importance these observations to the routine, clinical use of isosor- de dinitrate is not known. It may be prudent to gradually thdraw patients from ISDN when the therapy is being rminated, rather than stopping the drug abruptly.

formation for Patients: Patients should be told that the ıti-anginal efficacy of isosorbide dinitrate is strongly re- ted to its dosing regimen, so the prescribed schedule of ɔsing should be followed carefully. In particular, daily eadaches sometimes accompany treatment with isosorbide nitrate. In patients who get these headaches, the head- :hes are a marker of the activity of the drug. Patients ıould resist the temptation to avoid headaches by altering ıe schedule of their treatment with isosorbide dinitrate, nce loss of headache may be associated with simultaneous ıss of anti-anginal efficacy. Aspirin and/or acetaminophen, n the other hand, often successfully relieve isosorbide dini- ate-induced headaches with no deleterious effect on iso- ɔrbide dinitrate's anti-anginal efficacy.

reatment with isosorbide dinitrate may be associated with ghtheadedness on standing, especially just after rising rom a recumbent or seated position. This effect may be ıore frequent in patients who have also consumed alcohol.

)RUG INTERACTIONS

The vasodilating effects of isosorbide dinitrate may be addi- ive with those of other vasodilators. Alcohol, in particular, ıas been found to exhibit additive effects of this variety.

SDN acts directly on vascular smooth muscle; therefore, ıy other agent that acts on vascular smooth muscle can be xpected to have decreased or increased effect depending on he agents.

Marked symptomatic, orthostatic hypotension has been re- ɔorted when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class ɔf agents may be necessary.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of isosorbide dinitrate. In a modified two-litter reproduction study, there was no remarkable gross pathology and no altered fertility or gestation among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day.

Pregnancy: Pregnancy Category C: At oral doses 35 and 150 times the maximum recommended human daily dose, isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits. There are no adequate, well-controlled studies in pregnant women. Isosorbide dinitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether isosorbide dinitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide dinitrate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to isosorbide dinitrate are generally dose-related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator. Headache, which may be severe and persistent, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Cutaneous vasodilation with flushing may occur. Transient episodes of lightheadedness, dizziness, and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. (See OVERDOSAGE.)

Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred. (See OVERDOSAGE.)

Data are not available to allow estimation of the frequency of adverse reactions during treatment with SORBITRATE tablets.

OVERDOSAGE

Hemodynamic Effects: The ill effects of isosorbide dinitrate overdose are generally the results of isosorbide dinitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of the following: persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); initial hyperpnea; air hunger; and dyspnea, later followed by slow breathing and/or reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of isosorbide dinitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide dinitrate overdose.

There are no data suggesting what dose of isosorbide dinitrate is likely to be life-threatening in humans. In rats, the median acute lethal dose (LD_{50}) was found to be 1100 mg/kg (approximately 500 times the recommended therapeutic dose in humans).

No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide dinitrate and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of isosorbide dinitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide dinitrate overdose. Because the hypotension associated with isosorbide dinitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs and passive movement of extremities may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide dinitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8–6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

As noted above (**CLINICAL PHARMACOLOGY**), multiple studies with ISDN and other nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. Every dosing regimen for ISDN must provide a daily dose-free interval to minimize the development of this tolerance. To achieve the necessary nitrate-free interval with immediate-release oral ISDN, it appears that at least one of the daily dose-free intervals must be at least 14 hours long. In the case of sublingual and chewable tablets, it is probably true that one of the daily dose-free intervals must be somewhat longer than 14 hours.

As also noted above (**CLINICAL PHARMACOLOGY**), the effects of the second and later doses have been smaller and shorter-lasting than the effects of the first.

Large controlled studies with other nitrates suggest that no dosing regimen with SORBITRATE Tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

A patient anticipating activity likely to cause angina should take one SORBITRATE Chewable Tablet, 5 mg, about 15 minutes before the activity is expected to begin. SORBITRATE Sublingual Tablet, 2.5 mg to 5 mg, may be used to abort an acute anginal episode, but this use is recommended only in patients who fail to respond to sublingual nitroglycerin.

In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.

As with all titratable drugs, it is important to administer the minimum dose that produces the desired effect. The usual starting dose of SORBITRATE Oral Tablets is 5 mg to 20 mg, two or three times daily. For maintenance therapy, 10 mg to 40 mg, two to three times daily is recommended. Some patients may require higher doses. A daily dose-free interval of at least 14 hours is advisable to minimize tolerance. The optimal interval will vary with the individual patient, dose and regimen.

HOW SUPPLIED

SORBITRATE®Chewable Tablets USP

5 mg Chewable Tablets. (NDC-0310-0810) Green, round, scored tablets (identified front "S", reverse "810") are supplied in bottles of 100 and 500.

SORBITRATE Oral Tablets USP

5 mg Oral Tablets. (NDC-0310-0770) Green, oval-shaped, scored tablets (identified front "S", reverse "770") are supplied in bottles of 100 and 500 and Unit Dose 100.

10 mg Oral Tablets. (NDC-0310-0780) Yellow, oval-shaped, scored tablets (identified front "S", reverse "780") are supplied in bottles of 100, 500 and Unit Dose 100.

20 mg Oral Tablets. (NDC-0310-0820) Blue, oval-shaped, scored tablets (identified front "S", reverse "820") are supplied in bottles of 100 and Unit Dose 100.

30 mg Oral Tablets. (NDC-0310-0773) White, oval-shaped, scored tablets (identified front "S", reverse "773") are supplied in bottles of 100 and Unit Dose 100.

40 mg Oral Tablets. (NDC-0310-0774) Light Blue, oval-shaped, scored tablets (identified front "S", reverse "774") are supplied in bottles of 100 and Unit Dose 100.

Avoid storage at temperatures above 25°C (77°F).

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437

Rev P 02/98 SIC No. 64119-00

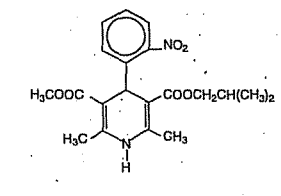
Shown in Product Identification Guide, page 346

SULAR®

(Nisoldipine)
Extended Release Tablets
For Oral Use

DESCRIPTION

SULAR® (nisoldipine) is an extended release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. Nisoldipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester, $C_{20}H_{24}N_2O_6$, and has the structural formula:



Nisoldipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 388.4. SULAR tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow release formulation and the core as a fast release formulation. SULAR tablets contain either 10, 20, 30 or 40 mg of nisoldipine for once-a-day oral administration.

Continued on next page

EXHIBIT 36

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639

2003/494
Seroquel
NDA 20-639

AstraZeneca Pharmaceuticals
Attention: Gerald L. Limp
Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp

Please refer to your new drug application (NDA) for Seroquel (quetiapine fumarate) Tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Seroquel can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

WARNINGS
Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are

starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/11/03 03:12:47 PM

EXHIBIT 37

AstraZeneca

Date: OCT 1 5 2003

Russell G. Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-120, Room 4049
1451 Rockville Pike
Rockville, MD 20852-1448

Re: NDA 20-639
SEROQUEL® (quetiapine fumarate) Tablets
Response to FDA Request for Labeling Change

Dear Dr. Katz:

The purpose of this submission is to acknowledge receipt of the September 11, 2003 correspondence from the Division of Neuropharmacological Drug Products which requests changes be made to the SEROQUEL label regarding the use of atypical antipsychotic medications and diabetes mellitus.

Earlier this summer, as part of our normal operating procedure, AstraZeneca completed a comprehensive internal analysis of existing data and concluded that the available data do not establish a causal link between diabetes and Seroquel. Among other things, our analysis is consistent with the Food and Drug Administration's position concerning the prevalence of diabetes in the general and schizophrenic populations. Moreover, we believe that the association between diabetes and schizophrenia further confounds the evaluation and interpretation of post-marketing reports and retrospective epidemiology studies that are already confounded by other factors such as lifestyle, weight, family history and other medications.

AstraZeneca is committed to working closely with the FDA to ensure that physicians receive accurate information to assist them in the appropriate prescribing of Seroquel. Currently, we are in the process of evaluating steps to address the concerns raised in the September 11, 2003 correspondence. Prior to taking any actions with respect to changing the Seroquel label, we would like to discuss such steps with the agency and ask that a meeting be scheduled in the first half of December 2003. I will be in contact with Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager in the near future to arrange such a meeting.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19850-8355

regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Brian Abbott, Regulatory Project Manager, at (302) 886-1437.

Sincerely,

Kevin McKenna, Ph.D.
Executive Director, Regulatory Affairs
Telephone: (302) 886-2742
Fax: (302) 886-3342

Technical Review Jacket: Steven D. Hardeman, RPh, HFD-120, Room 4028

EXHIBIT 38

AstraZeneca

IMPORTANT DRUG INFORMATION

April 22, 2004

Dear Health Care Provider,

In 2003, the Food and Drug Administration (FDA) asked all manufacturers of atypical antipsychotic medications, including AstraZeneca Pharmaceuticals LP (AstraZeneca), to add a Warnings statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL® (quetiapine fumarate) Tablets. AstraZeneca added the FDA Warnings statement to its SEROQUEL Prescribing Information and communicated that change to you in a letter dated January 30, 2004.

It has come to the attention of AstraZeneca that the Warnings statement set forth in its January 30, 2004 letter did not quote in its entirety the new Warnings statement included in the Prescribing Information; the words "and periodically during treatment" were omitted from the end of the second sentence of the second paragraph of the warning. Accordingly, enclosed is a new letter dated April 22, 2004, which quotes the Warnings statement from the Prescribing Information in its entirety.

Please discard the January 30, 2004 letter and replace it with the enclosed letter.

Sincerely,

W. Macfadden MD

Wayne Macfadden, MD
US Medical Director, SEROQUEL

219669

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437

Tel 302 886 3000
www.astrazeneca-us.com

AZPH1001 (01/00)

AstraZeneca

IMPORTANT DRUG INFORMATION

April 22, 2004

Dear Health Care Provider,

AstraZeneca Pharmaceuticals LP would like to inform you of important labeling changes regarding SEROQUEL® (quetiapine fumarate). The FDA has asked all manufacturers of atypical antipsychotic medications, including AstraZeneca, to add a Warnings statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL. Accordingly, the SEROQUEL Prescribing Information has been updated with the addition of the following information:

WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437
Tel 302 886 3000
www.astrazeneca-us.com

AstraZeneca remains committed to providing you with the most current product information available for the management of your patients. You may immediately review the Warnings statement about hyperglycemia and diabetes mellitus in the SEROQUEL Prescribing Information by visiting the web site at www.Seroquel.com. Updated package inserts containing the additional hyperglycemia and diabetes mellitus information will accompany the medication in the near future and you should, of course, refer to the insert for full Prescribing Information.

As always, we request that serious adverse events be reported to AstraZeneca at 1-800-236-9933 or to the FDA MedWatch program at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or by e-mail at www.fda.gov/medwatch. For additional medical information about SEROQUEL, please call 1-800-236-9933 from 9:00 am to 5:00 pm EST, Monday through Friday.

Sincerely,

Wayne Macfadden, MD
US Medical Director, SEROQUEL

219669

EXHIBIT 39

AstraZeneca

Minutes

Chairman
Vikram Dev - VP and Head of CDS US

Date 08 June 2007

Page 1/2

Participants
Eileen Carey - SERM Manager
Barry Arnold – EU Qualified Person
Judy Zander - Ex Dir US Safety Surveillance
Leigh Jefferies – GDSP Seroquel IR
Ron Leong - TASL
Martin Brecher – MSD
Julia Manning – Legal
Eileen Ming – Epidemiology
Liza DeAnnuntis – GDSP Seroquel XR
Xiang Ni – DS Physician
Susanne Fors – GRAD
Kathryn Bradley – AD Regulatory Labeling
Lisa Boomazian – Surveillance
Eva Alam – Surveillance
Linda Warner – Surveillance
Nina Delillio – Surveillance
Tara Lee – Surveillance
Howard Hutchinson - CMO
Ihor Rak – VP Clin TA – NS
Sandi Raff – Sr Dir Clin Res
Kurt Engelman – Stat Sci Dir
Kevin Stansberry – Med Com
Kevin McKenna – Reg TA VP – NS
Jan Eriksson – Dis Med/Epi
Mikael Astrom – Stat Sci Dir
Henrik Andersson – Biostats
Kevin Carroll – Chief Statistical Expert
Hakan Revevtlid – Clin Sci
Bjorn Paulsson – Med Neuro Sci
Anders F Karlsson – Dis Med/Epi
Kristina Axe – Med Com

Secretary
Eileen Carey – SERM Manager

Apologies:
Michelle Dillone – Legal
Nina Sherak – Surveillance
Deborah Rolfe – Surveillance
Richard Hellmund – CIS
Janet Spiers-Alston – Global SERM Manager
Joachim Forsgren – VP CDS
Robert Williams – SERM Support
Stacy Forbes – SERM Administrator

Meeting date
08 June 2007

Location
Wilmington

Subject
SERM – Seroquel

Confidential

1. Glucose Dysregulation

Following a review of all clinical trial data, including studies D1447C00125, D1447C00126, and D1447C00127, epidemiology literature, and post-marketing data, SERM recommended adding the following to Section 4.4 Special warnings and special precautions for use:

> **Increases in Blood Glucose and Hyperglycemia**
> Increases in blood glucose and hyperglycemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see also section 4.8 Undesirable effects).

AstraZeneca
Mereside
Alderley Park
Macclesfield
Cheshire
SK10 4TG

Tel: +44 (0) 1625 582828
Fax: +44 (0) 1625 583074
www.astrazeneca.com

SERM also recommended adding the following to Section 4.8 Undesirable Effects.

Frequency	System Organ Class	Event
Common (≥1% - <10 %)	Investigations	Blood glucose increased to hyperglycaemic level*

***Footnote**
Fasting blood glucose ≥126 mg/dL or a non fasting blood glucose ≥200 mg/dL on at least one occasion.

ACTION: Surveillance (Lisa Boornazian) and Medical Communications (Kevin Stansberry) will write the Clinical Overview.
Priority: B
Signal Source: Internal
Number of Signals: 1
Clinical Overview author(s): Kevin Stansberry and Lisa Boornazian
Due date for readiness of draft CO: 13 June 2007
Core Data Sheet (CDS) author: Kathryn Bradley
Due date for CDS issue: 15 June 2007
Due date for Investigators Brochure issue: 31 July 2007

EXHIBIT 4

Unknown

From: Murray Michael MF
Sent: Thursday, March 23, 2000 11:55 AM
To: Jones Martin AM - PHMS
Cc: Mullen Jamie JA; Goldstein Jeffrey JM; Tumas John JA
Subject: HELP FW: Meta Analyses

Importance: High

Attachments: RE: Meta Analyses; RE: Meta Analyses; TD0004.doc; TD0005 version 2.doc

RE: Meta Analyses

Martin,
I think we need your help on this one. Can you please read the attached messages. Can me, you, Jeff, and Jamie discuss this in Paris. I don't understand why we got such vast differences in these anayses.
Thanks,
Mike

Mike Murray

Senior Product Strategist, SEROQUEL
1-800-456-3669 ext. 4328
michael.murray@astrazeneca.com

From: Tumas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

Here's the analyses that I got from Emma. I've also attached a message that I sent to her yesterday asking for clarification.

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo **and** haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own analysis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or telelconference) and discuss where to go from here. We need to do this quickly, because Schulz needs to get a draft ready for APA and he needs any additional analyses we can give him well before then.

Thanks,

John

RE: Meta Analyses

From: Westhead Emma EK
Sent: Wednesday, March 22, 2000 12:44 PM
To: Tumas John JA
Cc: Shadwell Pamela PG
Subject: RE: Meta Analyses

Hi John,

Some of the work you need has already been completed within the Commercial Support Team. I attach the relevant technical documents for your information.

TD0004.doc (94 KB) TD0005 version 2.doc (127 KB)

I've tried to summarise below our current position with this data:

CGI

- Meta-Analysis has been done by CST vs haloperidol (TD005). No superiority of Seroquel over haloperidol was seen - although we can claim we are 'as least as effective' as haloperidol'.
- Seroquel vs placebo. A meta-analysis has not been performed, this could be progessed with the CST.

BPRS

- Meta-analysis has been performed on BPRS total, anxiety item, factor I, factor V, hostility item, hostility cluster and mood cluster for those patients who were symptomatic at baseline (TD004). No superiority of Seroquel over haloperidol was seen - although we can claim we are 'as least as effective' as haloperidol'.
- A similar meta-analysis was performed vs placebo on the same items. Superiority of Seroquel over placebo was seen in this case.

SANS

- A meta-analysis of SANS scores has been done for placebo and is contained within the new promotional guide (available for the Handover). Superiority of Seroquel over placebo.
- I don't believe many haloperidol studies actually recorded SANS but will check this.

Hence, for the BPRS analysis we haven't covered all of the items suggested by Dr Schulz. However, given that we are seeing a consistent picture of similar efficacy to haloperidol, I don't think we would seen anything different when analysing the other individual items. It depends on your focus - would you be happy to state "as least as effective" as haloperidol.

I propose that we could progress the following:

- a meta-analysis of CGI, seroquel vs placebo
- consider wether SANS data was recorded in haloperidol studies
- Discuss with Dr Schulz the focus of the meta-analysis of BPRS/CGI vs haloperidol before any extra work is done to look at items not yet analysed.

Could you consider these proposals and also let me know what your exact deadline is? I'll need to feed this in against the current work being progressed within the CST.

Kind Regards - sorry for the lengthy reply!
Emma

From: Tumas John JA
Sent: 22 March 2000 15:42
To: Westhead Emma EK
Subject: FW: Meta Analyses

Hi Emma,

It seems that Martin will not be easy to reach during the next week or so. Do you have a feel for how doable the below is? Dr. Schulz is supposed to have a draft manuscript for us by APA in May and I expect he will need the below in order to do so.

Thanks,

John

From: Tumas John JA
Sent: Monday, March 20, 2000 1:39 PM
To: Jones Martin AM - PHMS
Cc: Westhead Emma EK; Goldstein Jeffrey JM; Gavin Jim JP
Subject: Meta Analyses

Dear Martin,

You may be aware that Jeff and I met with Drs. Shulz and Tandon in Chicago a couple of weeks ago to discuss a few review manuscripts. The one with Dr. Schulz was conceived as a result of the responder meta analyses that were used for his APA (and CPNP) abstracts. After formulating an outline for the manuscript, Dr. Shulz put together a list of other meta analyses that would be needed in order for him to progress the manuscript. Below is a list of additional analyses Dr. Schulz has requested. Could you let me know the feasibility of these requests?

I've attached a first draft of the poster for CPNP that I sent to Dr. Schulz.

Best regards,

John

Meta analyses comparing quetiapine to haloperidol and placebo:

1) Total BPRS
2) CGI
3) BPRS Factor scores, ie thought disorder, anxiety, depression, negative symptoms.
4) Individual BPRS items: hallucinatory behavior, suspiciousness, flattened affect.
5) SANS
6) Control for factors:
    a) age
    b) gender
    c) length of illness.

<<File: Schulz.doc>>

EXHIBIT 40

AstraZeneca

Date: 22 June 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry
5901-B Ammendale Road
Beltsville, MD 20705-12666

RE: NDA 20-639 and NDA 22-047
SEROQUEL® (quetiapine fumarate) Tablets
Supplement-Changes Being Effected in 30 Days

Dear Sir/Madam:

In accordance with 21 CFR 314.70, AstraZeneca Pharmaceuticals LP (AstraZeneca) is submitting a Changes Being Effected in 30 Days labeling supplement for SEROQUEL (quetiapine fumarate) Tablets, NDA 20-639. AstraZeneca would also like to apply the changes in this submission to SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets, NDA 22-047. The labeling is being updated due to a review of clinical trial data.

The data included in the updated label provide new information on SEROQUEL and hyperglycemia. The data presented are from three sources. Glucose data were examined from 1) two long-term trials investigating treatment with SEROQUEL and a mood stabilizer to maintain an effect in patients with bipolar disorder; 2) a 6-month trial in schizophrenic patients designed to specifically examine atypical therapy and glucose metabolism; and 3) the pooling of placebo-controlled trials where duration of SEROQUEL therapy was less than 12 weeks.

The 2 long-term trials of SEROQUEL are D1447C00126, entitled "A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients" and Trial D1447C00127, entitled "A Multicenter, Randomized, Parellel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Divalproex) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients" . These trials will be submitted as part of a supplemental NDA application in July 2007.

The 6 month trial D1441C00125, which was previously submitted to the Agency, is entitled "A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine, and Risperidone in the Treatment of Patients with Schizophrenia".

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The data from the pooled placebo-controlled trials has been submitted to FDA previously in several different applications.

AstraZeneca is also requesting a teleconference approximately 5-7 days before the 30-day review expires.

Changes to the labeling appear in the following sections:

WARNINGS, Hyperglycemia and Diabetes Mellitus: A cross reference to the ADVERSE REACTIONS, Hyperglycemia sub-section has been added.

ADVERSE REACTIONS, Laboratory Changes, a new sub-section under the heading "Hyperglycemia" has been added.

The following files have been included in this submission:

1. SEROQUEL Labeling History-outstanding labeling supplements that may affect the review of this Special Supplement-Changes Being Effected (CBE) Supplement.

2. SEROQUEL Labeling Text-annotated and non-annotated versions of the Final Printed Labeling, which reflect changes noted in the CBE.

3. Structured Product Labeling-The final printed labeling in SPL format

4. Supporting documentation- Glucose Dysregulation in Patients treated with SEROQUEL (quetiapine)

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 20June07. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Gerald Limp, Director at (302) 886-8017.

Sincerely,

Kathryn Bradley, Associate Director
Regulatory Affairs
Telephone: (302) 886-5622
Fax: (302) 886-3342

EXHIBIT 41

Rev: 10/07 SIC 30417-03

SEROQUEL

(quetiapine fumarate)

TABLETS

RX ONLY

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

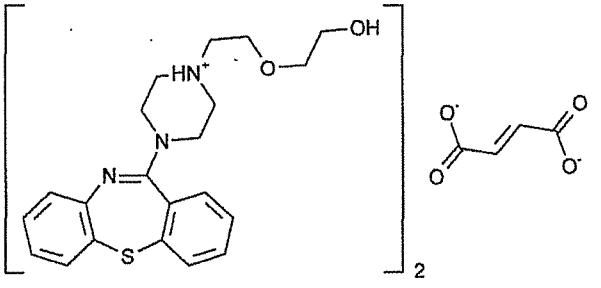
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. (See Warnings:

Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

SEROQUEL® (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.
Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg and 400 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and

adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of SEROQUEL in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.
SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn,

neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed

typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See Drug Interactions under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Disorder

Depression

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale with scores ranging from 0 to 60. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score. Improvement in symptoms, as measured by change in MADRS score relative

to placebo, was seen in both studies at Day 8 (week 1) and onwards. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS $\geq$ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an

adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the

BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

2. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Disorder

SEROQUEL is indicated for the treatment of both:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.

Depression

The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients (See **CLINICAL PHARMACOLOGY**). Effectiveness has not

been systematically evaluated in clinical trials for more than 8 weeks.

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy.

The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in

	Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are

experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine

phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel (see **ADVERSE REACTIONS, Hyperglycemia**). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Leukopenia, Neutropenia and Agranulocytosis: In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related

to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue SEROQUEL and have their WBC followed until recovery (See ADVERSE REACTIONS).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free

thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥240 mg/dL and triglycerides ≥200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have

shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo.

Potential for Cognitive and Motor Impairment:
Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are

reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo, (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%).

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and

Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**).

Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including SEROQUEL. Gradual withdrawal is advised.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families

and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Leukopenia/Neutropenia:

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL.

Laboratory Tests

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors. **(see PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum

plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of

other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25

to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that

might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories.

In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events

for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse events for bipolar depression.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo- Controlled Trials

Bipolar Disorder:

Depression: Overall, discontinuations due to adverse events were 12.3% for SEROQUEL 300 mg vs 19.0% for SEROQUEL 600 mg and 5.2% for placebo.

Mania: Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials.

Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/ Preferred Term	**SEROQUEL (n=719)**	**PLACEBO (n=404)**
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%

Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with

SEROQUEL was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%),

postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 4. Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression

Body System/ Preferred Term	**SEROQUEL (n=698)**	**PLACEBO (n=347)**
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
Respiratory, Thoracic, and Mediastinal		

Disorders		
Nasal Congestion	5%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

SEROQUEL

Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct

therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $<1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. **(See PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed.

Hyperglycemia

In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo.

In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥200 mg/dl was 1.7% and the incidence of a

fasting treatment-emergent blood glucose level ≥ 126mg/dl was 2.6%.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 2 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the

tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase

increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: *Frequent:* sweating; *Infrequent:* pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.
*adjusted for gender

Post Marketing Experience:
Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, and restless legs..
Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic

hormone secretion (SIADH), and Stevens-Johnson Syndrome (SJS).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (**See PRECAUTIONS: Orthostatic Hypotension**) One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

Management of Overdosage:

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative

should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Bipolar Disorder

Depression

Usual Dose: SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL	50 mg	100 mg	200 mg	300 mg

In the clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however, no additional benefit was seen in the 600 mg group.

Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of

25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one

side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

50 mg Tablets (NDC 0310-0278) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '50' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

400 mg Tablets (NDC 0310-0279) yellow, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '400' on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

• Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
• Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
• Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:
• thoughts about suicide or dying
• attempts to commit suicide
• new or worse depression
• new or worse anxiety
• feeling very agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse irritability
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?
• **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it.
Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

SEROQUEL is a trademark of the AstraZeneca group of companies

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA
Rev. 10/07 SIC 30417-03

EXHIBIT 42

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-036
NDA 22-047/S-001

AstraZeneca Pharmaceuticals LP
Attention: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated June 22, 2007, and July 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) extended-release tablets (NDA 22-047).

We additionally refer to an Agency letter dated January 8, 2008, requesting information on glucose abnormalities.

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

20-639/S-036 dated June 22, 2007
- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.

22-047/S-001 dated July 25, 2007
- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.
- Revisions to the **Adverse Reactions**-Postmarketing Experience section.
- Revisions to the **Drug Interactions**-P450 3A Inhibitors section.

We have completed our review of these supplemental applications, and they are approvable.

In general, the revisions made to the Postmarketing Experience and Drug Interactions sections are acceptable, and these comments were conveyed to you in an Agency letter dated May 13, 2008.

However, we are requesting the following changes to your proposed labeling (double underline font denotes additions and strike through font denotes deletions) before we can take a final action on these supplemental applications.

> *In 2 long-term placebo-controlled randomized withdrawal clinical trials, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) ~~for patients more than 8 hours since a meal~~ was 18.0 per 100 patient years for SEROQUEL (10.7% of patients)*

and 9.5 for placebo per 100 patient years (4.6% of patients). The mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo. Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of SEROQUEL on blood glucose may be underestimated.

For the 2 long term placebo-controlled bipolar maintenance trials, we are deleting the statement "more than 8 hours since a meal" from the proposed labeling language. In general, it does indicate fasting, but you indicated that there was still the possibility of caloric intake in the form of liquids or snacks. Therefore, since these subjects may not have been in a fasting state, this phrase should be deleted to reduce confusion.

Since the 2 long-term placebo-controlled bipolar maintenance trials studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with Seroquel and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. The mean increase in glucose from baseline was 2.70 mg/dl for SEROQUEL and 1.06 mg/dl for placebo.

For the 24 week active-controlled trial designed to evaluate glycemic status, you included only the LS mean data, and not the mean change from baseline to week 24 for the quetiapine group. Please provide us these data so that it can be incorporated into product labeling.

Based on the PLR regulations, your proposed addition of "Adverse Reactions, Vital Signs and Laboratory Studies, Hyperglycemia (6.2)" under RECENT MAJOR CHANGES in the Highlights should be deleted.

Additionally, we would refer you to our January 8, 2008 letter requesting information on the following glucose data. Please submit these information by the requested due date, June 30, 2008.

- Glucose mean and median change analyses of serum glucose levels by baseline values (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data)
- Fasting serum glucose post-treatment cut-off values are 140 mg/dL, 200 mg/dL, and 300 mg/dL
- Non-fasting serum glucose post-treatment cut-off value level is 300 mg/dL
- Observed case analyses of mean glucose change for the following specified exposure durations - 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks
- Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%

- Analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
6/25/2008 04:03:23 PM

EXHIBIT 43

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

DECLARATION OF WILLIAM C. WIRSHING, M.D.

1. My name is William C. Wirshing, M.D. I am competent to make this declaration and the facts stated herein are within my personal knowledge and are true and correct.

2. I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectric systems). I received my M.D. from the University of California at Los Angeles in 1982, graduating with a 3.97 G.P.A. and receiving the Sandoz Awared for "Excellence in the Behavioral Sciences." I remained at UCLA for both my rotating internship, during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency was at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia.

3. I am the Vice-President in charge of research and continuing medical education for Exodus Inc. in Culver City, California and also Clinical Director of Exodus Real Recovery in Agoura Hills, California. In my clinical psychiatric practice, I see approximately 325 new patients in a typical month; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students.

4. Over the decades between 1986 and 2006, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. I have attached my curriculum vitae and the report I submitted to counsel for Plaintiffs in this litigation as Exhibits A and B respectively, and I incorporate those documents by reference herein.

5. In my 25-plus years of clinical and research experience, I have had countless, significant, and frequent opportunities to read, review, and apply to my clinical practice with patients the information contained on FDA-approved prescription medicine labels/package inserts. I am particularly familiar with the warnings and other labeling information accompanying a class of antipsychotic medications commonly referred to as second generation antipsychotics such as risperidone ("Risperdal"), olanzapine ("Zyprexa"), ziprasidone ("Geodon"), aripiprazole ("Abilify"), and quetiapine (Seroquel).

6. With particular respect to Seroquel's 1997-to-present label concerning weight gain, it is my opinion that, rather than adequately "warn" about the 23%-33% or higher risk

of statistically significant weight gain that AstraZeneca observed in clinical trials of Seroquel, the company obscured and buried the weight gain data and, more importantly, the effect of the data by putting it in the "adverse reaction" section of the label. AstraZeneca has never "warned" about weight gain because the necessary information concerning weight gain is not clearly stated in the "warnings" section of the label. As a practicing clinician, it is unclear, ambiguous, and misleading to prescribing doctors for the single most prominent serious toxic characteristic of this drug (statistically significant weight gain) not to be included in the "warnings" section of the label where a prescribing physician would expect to find such information. The "adverse reactions" section on the package insert is near the end of the labeling, very often several dozen paragraphs following the "warnings" section, and is akin to a laundry list. In practice, it is quite simply not given the same attention or priority by prescribers as the "warnings" and "precautions" sections near the beginning of the label. Therefore, the warning given regarding weight gain is inadequate. As shown by the true and correct copy of the Physicians' Desk Reference section on Seroquel from 2004, attached as Exhibit C, the highlighted weight gain information is dwarfed by the overwhelming balance of other information about the drug.

7. The 1997-to-present Seroquel label is also unclear, inaccurate, and misleading because weight gains of the magnitude that Seroquel causes, according to its own label and the company's data, are impressively large and impact an amazingly large and consistent percentage of patients. The serious and frequently deadly health consequences associated with weight gain (namely hyperglycemia and diabetes mellitus, and complications therefrom) necessitated adequate warning. Such warning should have appeared in the "warnings" not

"adverse reactions" section of the label. Placement of the weight gain clinical trials data in the "adverse reactions" section inadequately conveys to prescribing physicians the severity of the health consequences associated with a 23%-33% or more weight increase associated with Seroquel treatment, further rendering the inclusion of such data in the adverse reactions section inadequate. Additionally, the label fails to describe any of the health consequences for which weight gain creates an increased risk—i.e., hyperglycemia and diabetes mellitus, among other serious and potentially lethal health concerns including increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). To put it another way, the labeling fails to state a "cause and effect" relationship between the statistically significant weight gain accompanying Seroquel use and the increase in glucose dysregulation that was also revealed by AstraZeneca's clinical trials and company data that I have reviewed.

8. Regarding AstraZeneca's marketing materials during this same period with respect to weight gain, as well as sales representatives' direct messages (discussions) to physicians, the materials that I have reviewed, including Doctor Brecher's 2000 article and Doctor Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or had favorable weight profiles. Sales materials profiling patient experiences with Seroquel by a Doctor Reinstein, which I have reviewed, implied that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. Further, despite information identifying weight gain as a dose-dependent side effect, AstraZeneca has repeatedly stated in its sponsored literature and marketing material that I reviewed (e.g., the Brecher and Nasrallah

articles) that there is no dose-dependent relationship between Seroquel and weight gain Other marketing messages included claims that Seroquel is "weight neutral" or causes "minimal weight gain," further obscuring and diluting the severity of any mention of clinically significant weight gain in the label's adverse reaction section. At best, such promotional messages further render the so-called "adverse reaction" regarding seriously hazardous weight gain unclear and ambiguous because on the one hand, the label and company data revealed that 23%-33% or more of Seroquel users will experience clinically significant weight gain, but the sales message was that the drug is "weight neutral" causes "minimal weight gain" or has a "favorable weight profile." These sales messages not only contradicted what AstraZeneca knew about weight gain and Seroquel, from my review of Seroquel clinical trial data and company documents, they actually contradicted Seroquel's own approved label, undermining the clarity, accuracy, and unambiguousness of the label.

9. With respect to the pre-2004 label concerning hyperglycemia and diabetes mellitus, it is my opinion that AstraZeneca obscured and buried any mention of hyperglycemia and diabetes in the pre-2004 label by simply mentioning those words and characterizing the conditions as "infrequent" in the adverse reactions section of the label. AstraZeneca further obscures and confuses the issue by also listing "hypoglycemia" and "weight loss" as "infrequent" adverse reactions. This is simply no warning at all as to the true frequency and severity of those side effects suffered by Seroquel users. Documents I have reviewed showed that the company knew, prior to Seroquel's launch, that statistically significant weight gain increases by Seroquel users, would seriously impact patient health in terms of glucose dysregulation. Moreover, at least by 2000, documents I reviewed showed

that the company's medical safety director had concluded that Seroquel can cause impaired glucose dysregulation including diabetes.

10. The pre-2004 label is inadequate to warn prescribing physicians of the nature, severity, and frequency of the risk of hyperglycemia and diabetes mellitus associated with Seroquel, and for the above reasons is unclear, inaccurate, and ambiguous. It does not convey in a meaningful way the toxic potential of the drug and is confusing.

11. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined any attempt by AstraZeneca to warn of hyperglycemia and diabetes mellitus in the pre-2004 label. For example, Dr. Nasrallah's 2002 paper cites a now discredited study by Dr. Reinstein suggesting that Seroquel patients lost weight and had their diabetes cured after taking Seroquel for ten weeks.

12. With respect to the 2004-2007 label for Seroquel regarding hyperglycemia and diabetes mellitus, the so-called "class label" warning section on hyperglycemia and diabetes is inadequate, unclear, and ambiguous because it is laced with generalities, disclaimers, and distracting verbiage. Specifically, it fails to accurately and clearly state the measured increases in new onset diabetes that are specific to Seroquel, which were significantly greater based on clinical trials and company documents that I have reviewed as compared to certain other second generation antipsychotics that also bear the class label warning.

13. Moreover, the class label neglects to accurately describe the level of Seroquel's risk of those side effects, which was extraordinary according to the clinical trials

and company documents that I have reviewed and as compared to second generation antipsychotics such as aripiprazole and ziprasidone, which studies show do not cause clinically significant weight gain and hyperglycemia/diabetes. Instead, the 2004-2007 label describes merely that hyperglycemia and related serious complications "has been reported" without any data whatsoever quantifying the rate of incidents and severity of such risks and complications, or identifying which second generation antipsychotics were the subject of such "reports." The label language then further waters down the "warning" by indicating that measurement of glucose abnormalities is complicated by factors such as an increased rate in diabetes among the schizophrenic or general populations. This warning is far from a model of clarity and unambiguousness given the conclusions that the company and other foreign regulatory bodies reached that a reasonable association between Seroquel and hyperglycemia/diabetes (if not a causal association as well) had already been established before and during the time period this label was in effect.

14. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined and diluted the warning. For example, company documents reveal that physicians were still receiving correspondence from the company referencing the Reinstein study concluding that Seroquel may cause weight loss and reverse diabetes in sizeable numbers of patients. Other internal company communication revealed that the Brecher article was still being disseminated. The FDA also reprimanded AstraZeneca in 2006 for failing to disclose in promotional material the increased risk of hyperglycemia and diabetes mellitus in patients treated with Seroquel, resulting in the promotional material being "misleading" and "undermin[ing] the warning."

15. Based on clinical experience, the so-called class label warning is inadequate to communicate the true nature and severity of the hyperglycemia/diabetes mellitus risk associated with Seroquel alone to physicians prescribing Seroquel to their patients.

16. Additionally, based on documents I have reviewed, language associated with the class label warning was a product of negotiations between AstraZeneca and the FDA. For example, with respect to the January 2004 "Dear Doctor" letter relative to the "class label" warning sent by AstraZeneca, earlier correspondence between the FDA and AstraZeneca revealed that AstraZeneca desired to characterize the new "warning" as simply being "about hyperglycemia and diabetes in patients taking these medications," but the FDA stated that it "preferred" the statement "describing increased risk of hyperglycemia and diabetes in patients taking these medications." From the correspondence I reviewed, it appears as though AstraZeneca determined not to further press the issue with the FDA.

17. With respect to the label change that occurred in 2007 regarding the hyperglycemia and diabetes mellitus warning contained on Seroquel, while it directs one to new language in the "adverse events" section, it is my opinion that the 2007 label change is still inadequate because it fails to clearly, accurately, and unambiguously describe the alarming rate at which Seroquel users in long-term clinical trials contracted diabetes, and the necessary warning language that a prescribing physician would expect to see relative to that very significant risk is not contained in the "warnings" section. Instead mere cross-reference is made to clinical trials data the "adverse reactions" section. The "adverse reactions" section does not mention the word "diabetes," but examination of the data reveals that Seroquel patients in long-term clinical trials were over twice as likely to suffer diabetes than

patients taking placebo. Company documents that I have reviewed show that AstraZeneca has characterized the risk of diabetes-level blood glucose abnormalities associated with Seroquel as "common." The label is facially unclear, inaccurate, and misleading because the frequency and severity of the diabetes risk is not mentioned in the "warnings" section but instead is buried in the "adverse reactions" section, and because what is truly diabetes-level blood sugar is characterized merely as "hyperglycemia" and "increased blood sugar"—i.e., fasting blood glucose measurements (those taken 8 hours after a meal) that are $\geq$ 126 mg/dL or non-fasting blood glucose measurements $\geq$ 200 mg/dL is frank diabetes, not merely hyperglycemia. The label is also inadequate because it fails to clearly and unambiguously warn of a "cause and effect" relationship between Seroquel use and diabetes-level blood glucose abnormalities.

18. The FDA is not satisfied with AstraZeneca's most recent Seroquel label change, as indicated in the June 2008 correspondence I have reviewed from the FDA to AstraZeneca. The FDA requested that the updated label be changed to add the additional information that "[t]he mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and –0.05 mg/dl for placebo," indicating that the FDA desires for AstraZeneca to reveal that there was more than a 5-fold increase in blood glucose levels between those subjects taking Seroquel and those taking placebo. The FDA also asked that AstraZeneca add the statement: "Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of Seroquel on blood glucose may be underestimated." In its letter, the FDA supported the additional statement above as follows:

> Since the 2-week long-term placebo-controlled bipolar maintenance trial studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

Thus, the FDA wanted to provide clarity that the already negative blood glucose results stated in the new label—based on studies that effectively prescreened participants who did not well-tolerate Seroquel—actually may be even worse than the label reveals. AstraZeneca has not made the labeling changes that the FDA has requested as of the date of execution of this Declaration. AstraZeneca's evasive treatment and abstruseness with respect to this label change further confirms my opinion that AstraZeneca has not been forthright with physicians who prescribe Seroquel in the sense of "full disclosure" of pertinent, potentially life threatening (or certainly life-altering) healthcare information such that physicians may fully consider the risks and benefits and adequately advise and consult with their patients.

19. Overall, the inadequacy of Seroquel's labeling and accompanying misstatements of the risks associated with its use make it prohibitively difficult for a physician relying on such information to appreciate the true nature of Seroquel's risks and discuss those risks with his or her patients.

20. Furthermore, in my opinion, AstraZeneca's warnings for Seroquel appear to have been designed to obscure known risks associated with the drug, rather than to clearly, accurately, and unambiguously communicate risks to prescribing physicians in a frank,

explanatory manner such that they would have ready access to such critical information in treating their patients.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this the 19th day of November, 2008.

William C. Wirshing, M.D.

CURRICULUM VITAE

WILLIAM C. WIRSHING, M.D.

Address

Work: Exodus Recovery Acute Treatment Center
3828 Delmas Terrace
Culver City, CA 90232

Tel (310) 253-9494

Home: 6433 Topanga Canyon Blvd. #429
Woodland Hills, CA 91303

Tel (310) 413-4200
Home Fax (818) 595-1367

E-mail: WIRSHING@UCLA.EDU

Birthdate 11 June, 1956

Birthplace Palo Alto, CA

Education

1982 M.D. - UCLA

1978 B.S. Electrical Engineering & Computer Science, University of CA, Berkeley

Internship, Residency, & Fellowship

1986-88 Postdoctoral Research Fellowship in Schizophrenia Research, UCLA, Department of Psychology, Los Angeles, CA

1983-86 Resident in Psychiatry, UCLA Neuropsychiatric Institute, Los Angeles, CA

1982-83 Intern in Medicine, UCLA Center for the Health Sciences & Wadsworth VA Medical Center, Los Angeles, CA

Licensure

1983 California License No. G 50986, DEA No. FW0654447

Certification

1991 Added Qualification in Geriatric Psychiatry, American Board of Psychiatry and Neurology (#000479)

1988 Diplomat, American Board of Psychiatry and Neurology (#30125)

Academic Appointments/Positions

2008- Medical Director Real Recovery. Agoura Hills, CA

2007- Vice President in charge of continuing medical education and research Exodus Corp. Los Angeles, CA

1996-06 Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1993-06 Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1993-96 Associate Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1987-06 Director, Brentwood Movement Disorders Laboratory, West Los Angeles VA Medical Center

1988-93 Co-Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1986-93 Adjunct Assistant Professor of Psychiatry, Department of Psychiatry & Biobehavioral Sciences, UCLA School of Medicine

1986-88 Postgraduate Research Scholar, Department of Psychology, UCLA

1986-88 Co-Chief, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center

1985-86 Chief Resident, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center, Brentwood Division

Awards & Honors

2006 Nominated for Golden Apple Award for Clinical years by graduating class of 2006

2003 Award in Recognition of Dedication in Teaching Excellence from the Graduating Class of 2003, David Geffen School of Medicine at UCLA

1999 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1999 Lucien B. Guze Golden Apple Award for Outstanding Teaching Class of 2001, UCLA School of Medicine

1998 Certificate of Excellence, West Los Angeles Success 98 Award Program, West Los Angeles Veterans Administration Medical Center

1996 Distinguished Educator Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1994 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1993 UCLA Medical School. Class of 1995 - Outstanding Teacher Award

1991 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1988 Travel scholarship to attend the 4th Biannual Workshop on Schizophrenia in Badgastein, Austria.

1982 Sandoz Award for Excellence in the Behavioral Sciences

1982 Alpha Omega Alpha

1978 Tau Beta Pi (Engineering National Honor Society)

1978 Phi Beta Kappa

1978 B.S. Summa Cum Laude

Major Teaching Experience

2007- Weekly Continuing Medical Education Lecture Exodus Urgent Care Center, Culver City, CA.

2000-06 Case Conference: Diagnostic Dilemmas - Psychiatry (#425 Sec. 5) This weekly case conference focuses on differential diagnosis, with an emphasis on the various etiologies of psychotic symptoms including schizophrenia, substance-induced psychosis, malingering,and other disorders.

1995-06 Movement Disorders Seminar - Psychiatry (#446) a weekly, clinical based, interactive seminar focusing on the examination and treatment of patients with a broad range of movement disorders for psychiatry residents,

	neurobehavior fellows, medical students, and research staff (with DA Wirshing, M.D., CS Saunders, M.D., and JM Pierre, M.D.). (1.5 hrs/week)
1992-2004	Course director - Psychopathology (#201) for 2nd-year medical students. (6 hrs/week)
1991-2002	Faculty sponsor - Student Research Program. (1-8 hrs/week)
1990-1992	Faculty advisor for biweekly seminar for psychiatry residents on critical reading of the literature (with Joel Yager, MD, and Alison Doupe, MD, PhD). (1 1/2 hrs/2 weeks)
1989-92	Movement Disorders Seminar (Psychiatry Course #453), a weekly forum for psychiatry residents, neurobehavior fellows, and medical students (with JL Cummings, MD). (1 hr/week)
1988-1991	Class Organizer/Lecturer of "Topics in Geropsychiatry", a weekly seminar for psychiatry residents, medical students, and psychology interns. (1 1/2 hrs/week)
1988-06	Ward teaching supervisor (Psychiatry Course #403) for 1st- and 3rd-year psychiatric residents and for 3rd- and 4th-year medical students on the Schizophrenia Treatment Unit, BVAMC. (9 hrs/week)
1986-06	Off-ward teaching supervisor (Psychiatry Course #403) for 1st-, 2nd-, and 3rd-year psychiatric residents in the UCLA Residency Training Program. (2-4 hrs/week)
1986	Lecturer: "The Psychiatric Hospital in Historical Perspective" (with Dora B Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.
1985-88	Ward teaching supervisor for first- and second-year psychiatric residents and for first-year geriatric medicine fellows on the Geropsychiatry Ward, WLA/VAMC.
1985	Lecturer: "The Historical Roots of Modern Medicine" (with Dora Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.

Hospital/University Committees

2005-06	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
2000-02	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1999-03	Medical Student Education Strategic Planning Committee
1999-02	Human Subjects Protection Committee, Veterans Affairs
1998	Neuroscience Sub Committee, UCLA School of Medicine
1997- 00	Faculty Executive Committee
1997- 01	Voluntary Clinical Faculty Academic Appointments and Adjustments Committee

1996-99	Second Year Curricular Block Planning Committee, UCLA School of Medicine
1995-98	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1992-94	Ad Hoc Committee for Dementia, UCLA School of Medicine
1992-96	Student Affairs Committee, UCLA School of Medicine
1992-94	Human Subjects Protection Committee, Veterans Affairs
1991-93	Residency Fellowship Nominating Committee, UCLA
1991	Chief of Psychiatry Search Committee, Veterans Affairs
1990-93	Residency Education Curriculum Committee, UCLA
1988-90	Human Subjects Protection Committee, Veterans Affairs
1988-03	Pharmacy and Therapeutics Committee, Veterans Affairs

Grants Awarded

2005-06 "Management of Antipsychotic Medication Associated Obesity"
Co-Principal Investigator Donna A. Wirshing, M.D. PI
VA Merit Review

2005-06 "Relapse Prevention: Long Acting Atypical Antipsychotics"
Co-Investigator , Donna A. Wirshing, M.D. PI
NIMH RO1 (Multicenter Collaborative)

2002-05 Veterans Affairs Merit Review
"Cigarette Smoking by Schizophrenic Patients (Phase II)"
Collaborator. Jarvik Murray, M.D., Ph.D. - P.I.

2000-02 National Institute of Mental Health, MH41573-11A1
"Management for Risk of Relapse in Schizophrenia"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

2000-03 National Institute of Mental Health, MH59750-01A1
"Treatment of Negative Symptoms and Cognitive Impairments"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1998-00 Veterans Affairs Merit Review
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-02 Veterans Affairs Merit Review
"Quetiapine vs. Haloperidol Decanoate for the Long-Term Treatment of Schizophrenia and Schizo-Affective Disorder"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1995-98 National Institute of Health, 1R01-DA09570-01A1
"Dopaminergic Modulation of Nicotine Reinforcement"
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1995-99 National Institute of Health, 1R01-MH46484-01
"New Antipsychotics: Clinical Trials and Naturalistic Follow-up."
Co-Investigator. Stephen R Marder, MD - P.I.

1993-95 Veterans Affairs Merit Review to examine cigarette smoking by schizophrenic patients.
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1993-96 Veterans Affairs Merit Review to examine the risks and benefits of typical and atypical antipsychotic drugs in the treatment of acute psychotic episodes.
P.I.

1992-95 National Institute of Health: MH46484-03
"Clozapine - Treatment Response and Disability."
Co-Investigator.

1990-92 NARSAD (National Alliance for Research on Schizophrenia and Depression) Young Investigators Grant to develop a method of quantifying drug-induced akathisia and to apply this method of determining the relative akathisic liability of the atypical neuroleptic clozapine.

1986-05 National Institute of Health: MH41573
"Management of Risk of Relapse in Schizophrenia."
Co-Investigator. Stephen R Marder, MD and Robert P. Liberman, MD Co-P.I.s

1988-90 Veterans Affairs Merit Review to examine the feasibility of using a battery of electromechanical instruments to prospectively follow patients with tardive dyskinesia.
Co-Investigator. JL Cummings, MD, P.I.

1988-89 NARSAD Young Investigators Grant to continue research on the instrumentation of drug-induced movement disorders.

1987-88 Biomedical Research Support Grant from the Department of Psychiatry, UCLA School of Medicine, to develop a system to measure and analyze the movements of the human larynx.

Industry Sponsored

Investigator Designed and Initiated

1999-03 Janssen Pharmaceutica: Investigator designed protocol.
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

2000-05 Eli Lilly, Inc.: Investigator designed protocol.
"Olanzapine vs. Risperidone in Treatment Refractory Schizophrenia"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

Industry Designed and Initiated

1998-99 Merck & Company, Inc.
"A Double-Blind, Active and Placebo-Controlled, Safety Tolerability, and Preliminary Antipsychotic Activity Study of MK-0869 in Hospitalized Schizophrenia Patients"
P.I. William C. Wirshing, M.D.

1998-99 Hoechst Marion Roussel, Inc.
"A Multicenter, Placebo and Active Control, Double-Blind Randomized Study of the Efficacy, Safety and Pharmacokinetics of M100907 (10 and 20 mg/d in Schizophrenic and Schizoaffective Patients."
Co-Investigator. Donna A Wirshing, M.D. - P.I

1997-00 Organon 041002
"A Double Blind, Five-Armed, Fixed Dose, Active and Placebo Controlled Dose-Finding Study With Sublingual ORG 5222 in Subjects With Acute Phase Schizophrenia"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 42,776
"An Open Label Follow-on Study on the Long-Term Safety of Aripiprazole in Patients with Psychosis"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 31-97-202
"A Phase III Double-Blind Study of Aripiprazole and Risperidone in the Treatment of Psychosis"
P.I. William C. Wirshing, M.D.

1997-98 Janssen Pharmaceutica: RIS-USA-112
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-99 Janssen Pharmaceutica: RIS-USA-113
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1995-98 Hoechst Marion Roussel
"An Open-Label, Follow-Up, Multicenter, Long-Term Maintenance Study of MDL 100, 907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-98 Otsuka: 31-95-201
"OPC-14597: An Open-Label Tolerability Study in Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1995-96 Hoechst Marion Roussel: IND# 47,372
"A Randomized, Double-Blind, Placebo-Controlled, Parallel, Multiple Dose, Multicenter Study to Determine the Safety, Tolerability, Pharmacokinetics, and Biochemical Activity of MDL 100,907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-96 Merck & Company, Inc.
"A Double-Blind, Placebo-Controlled, Safety, Tolerability and Preliminary Antipsychotic Activity Study of L-745,870 in Hospitalized Schizophrenic Patients"
P.I. William C. Wirshing, M.D.

1995-96 Otsuka: 31-94-202
"A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1993-97 Eli Lilly Incorporated: F1D-MC-HGAP
"Fixed Dose Olanzapine versus Placebo in the Treatment of Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-99 Pfizer, Inc.: 128-116B
"A 52-Week, Open Extension Study Evaluating the Safety and Outcome of 40-80 mg BID of Oral Ziprasidone (CP-88,059-1) Daily in the Treatment of Subjects Who Have Participated in Previous Ziprasidone Clinical Trials."
Co-Investigator. Donna Ames, M.D. - P.I.

1993-94 R.W. Johnson: M92-083
"Multi-Center, Randomized, Double-Blind, and Controlled, 4 Week, Multiple Oral Rising Dose Study to Determine Safety Tolerability, Pharmokinetics and Behavioral Activity of RWJ-37796 in Male Schizophrenic Subjects Phase II."
P.I. William C. Wirshing, M.D.

1992-98 Abbott Laboratories - Neuroscience Venture: M92-795
"An Open Label Assessment of the Long Term Safety of Sertindole in the Treatment of Schizophrenic Patients."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-96 Pfizer, Inc.: 128-115
"Phase III, Six Week, Double Blind, Multi-Center, Placebo Controlled Study Evaluating the Efficacy and Safety of Three Fixed Doses of Oral Ziprasidone (CP-88,051-1) and Haloperidol in the Acute Exacerbation of Schizophrenia and Schizo-Affective Disorder."
Co-Investigator. Donna Ames, M.D. - P.I.

1992-94 Glaxo, Inc.: S3B-201
"A Randomized, Double-Blind, Placebo-Controlled, Crossover Evaluation of the Effects of GR68755C on Serum Levels of Haloperidol in Patients with a Diagnosis of Schizophrenia."
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1992-93 Abbott Laboratories - Neuroscience Venture: M92-762
"A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Sertindole in Schizophrenic Patients."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1992-93 Schering Plough Research Corporation: SCH39166
"Safety, Tolerance and Pilot Efficacy of Rising Multiple Doses of SCH39166: An Open Label Trial."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1988-89 Astra Pharmaceuticals
"Raclopride in Schizophrenia: a Haloperidol-Controlled, Double-Blind, Dose-Finding Clinical Trial."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

1990-91 Sandoz Pharmaceuticals
"A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Multi-Stage, Dose-Finding Study of SDZ HDC 912 in DSM-III-R Defined Hospitalized Schizophrenic Patients."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

Reviewer / Editor

Reviewer:

American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Brain Dysfunction
CNS Spectrums
Comprehensive Psychiatry

International Journal of Psychiatry in Medicine
Journal of Clinical Psychiatry
Journal of Psychiatric Research
Journal of Clinical Psychopharmacology
Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Psychiatry Research
Psychopharmacology
Psychopharmacology Bulletin
Psychosomatics
Schizophrenia Bulletin

Invited Presentations

04/07 "Schizophrenia and Related Psychoses" Grand Rounds Northridge Hospital, Northridge CA 15 Apr 2007

08/06 "Tailored Management of Schizophrenia in the Real World: A Naturalistic Approach" Presented at Evansville State Hospital, Evansville, IN, 17 Aug 06

08/06 "The Metabolic Mayhem of Atypicals: The TD of the New Millennium" Grond Rounds Antelope Valley Hospital 11 Aug 06.

08/06 "Use of Atypical Antipsychotics in Bipolar Illness"1 Aug 06 Honolulu, HI.

03/06 "Treatment of Agitation with Behavioral Interventions and Atypical Antipsychotics in Schizophrenia" Presented at American Association for Geriatric Psychiatry, San Juan, Puerto Rico, 11 Mar 06.

02/06 "Addressing Metabolic Disturbances with Antipsychotic Treatments" Presented at San Francisco General Hospital, Dept of Psychiatry, San Francisco, CA, 24 Feb 06

12/05 "Metabolic Impact of Atypical Antipsychotics: The View from Two Decades of Experience" Presented at Eden Medical Center, Castro Valley, CA 7 Dec 2005

11/05 "Clinical Management of Behavioral and Psychological Symptoms in Dementia" Presented at Salem Hospital, Salem, OR, 16 Nov 05

10/05 "Marketing Atypical Antipsychotics and the Opacity of Adiposity" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 26 Oct 05

07/05 "Treatment of Agitation in Elderly Demented Patients" Presented at Grand Rounds, Hawaii State Hospital, Kaneohe, HI, 12 Jul 05

07/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 12 Jul 05

04/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Battle Creek VA Med Center, Battle Creek, MI, 7 Apr 05

12/04 "Considerations in Long-Term Management of Schizophrenia" Presented at Grand Rounds, Corcoran State Prison, Corcoran, CA 1 Dec 04

12/04 "Management of Associated Comorbidities of Schizophrenia" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA 1 Dec 04

09/04 "Pharamacological Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Scripps Mercy Hospital, San Diego, CA, 7 Sep 04

08/04 "Metabolic Disorder" Presented at Grand Rounds, Kedren Hospital, Los Angeles, CA 16 Aug 04

06/04 "Atypical Antipsychotics in Special Populations" Presented at Grand Rounds Terrell State Hospital, Terrell, TX, 21 Jun 04

06/04 "The Many Faces of 'Wartime' PTSD" Presented at Grand Rounds, Mountain Crest Hospital, Fort Collins, CO, 15 Jun 04

05/04 "Pharmacology Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Utah State Hospital, Provost, UT, 20 Mau 04

05/04 "Psychiatric Research Ethics" Presented at NIH Neuroscience Center, Bethesda, MD, 17 May 04

05/04 "Lab Science to Clinical Practice: Neurochemical Model of Antipsychotic Effects" Presented at Grand Rounds, Metropolitan State Hospital, Norwalk, CA, 12 May 04

04/04 "New Indications for Antipsychotics for Bi-Polar Disorders" Presented at Grand Rounds, Cedars Sinai, Los Angeles, CA, 29 Apr 04

03/04 "A Century after Bleuler, What Do We Really Know About Schizophrenia, Its Origin, Cause, and Treatment?" Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

03/04 "The Antipsychotics: Their Developmental History, Clinical Limitations, Major Toxicities, and Anticipated Future." Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

02/04 "Consideration in the Long-term Management of Schizophrenia" Presented at Grand Rounds, Stanford University Hospital, Stanford, CA, 19 Feb 04

02/04 "The Marketing of Atypical Antipsychotic Drugs: A War for Our "Loyalties" Moves Into its Guerilla Phase" Presented at Grand Rounds, Sepulveda VA Mental Health Center, Los Angeles, CA, 11 Feb 04

02/04 "Drug Induced Metabolic Symptoms with Antipsychotic Paradigm Shift in an Approach to Patient Care" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 4 Feb 04

01/04 "Risperdal Consta" Presented at Grand Rounds, Indianapolis VA, Indianapolis, IN, 15 Jan 04

12/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Riverside County Department of Mental Health, Hemet CA, 9 Dec 03

12/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 2 Dec 03

11/03 "Monitoring Patients on Antipsychotic Drugs for Glucose Intolerance and Other Features of the Metabolic Syndrome" Presented at Alexandria, VA, 19-20 Nov 03

11/03 "Antipsychotics: Overcoming Side Effect Treatment Barriers" Presented at Grand Rounds, Long Beach VA Medical Center, Long Beach, CA, 12 Nov 03

11/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Fresno, CA, 11 Nov 03

11/03 "A Broad Spectrum in Psychotropics" Presented at Grand Rounds, Golden Valley Health Center-Corner of Hope, Modesto, CA, 6 Nov 03

10/03 "The Mechanistic Similarities and Distinctions Among Antipsychotics: A Treatment Refractory Model" Presented at Grand Rounds, Hawaii State Hospital Auditorium, Oahu, HI, 24 Oct 03

10/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, San Francisco Clinic, San Francisco, CA, 4 Oct 03

10/03 "Kaiser/Group Health Cooperative AP Advisory Board" Presented at San Francisco, CA, 4 Oct 03

10/03 "Improvement in Cognitive Function, Dosing and Titration" Presented at Grand Rounds, Olive View Hospital, Sylmar, CA, 2 Oct 03

09/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Seattle Hospital, Seattle, WA, 11 Sep 03

08/03 "Neurocognition and Schizophrenia Including Issues on Nicotine Receptors" Presented at Grand Rounds, Ventura County Behavioral Health Inpatient Unit, Ventura, CA, 13 Aug 03

05/03 "Switchover from Clozapine to Quetiapine: Mixed Results" Presented at Biological Psychiatry, San Francisco, CA, 15 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, Eugene VA Clinic, Eugene, OR, 13 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, VA Medical Center, Portland, OR, 12 May 03

05/03 "Atypical Antipsychotics: Marketing Mischief or Metabolic Mayhem" Presented at Grand Rounds, Harbor-UCLA Medical Center, Torrance, CA, 6 May 03

04/03 "Metabolic Consequences of Antipsychotic Therapy" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 30 Apr 03

03/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, RJ Donovan Correctional Facility, San Diego, CA, 12 Mar 03

03/03 "Aripiprazole" Presented at Grand Rounds, Patton State Hospital, Patton, CA, 5 Mar 03

02/03 "Applied Neuropsychopharmacology: The Spectrum of Clinical Outcomes with Atypical Antipsychotics" Presented at the CNS Advisory Summit, Scottsdale AZ, 22 Feb 03

02/03 "The Use of Atypical Antipsychotics in Mood Disorders" Presented at Grand Rounds, Region IV Parole Headquarters, Diamond Bar, CA, 21 Feb 03

01/03 "Metabolic Side Effects of Atypical Antipsychotics" Presented at Grand Rounds, King Drew Medical Center, Los Angeles, CA, 28 Jan 03

01/03 "TD - What if Anything is New?" Presented at Grand Rounds, VA Hospital, Neurology Department, Los Angeles, CA, 24 Jan 03

01/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 22 Jan 03

12-02 "Aripiprazole" Presented at Grand Rounds, Loma Linda University, Redlands, CA 20 Dec 02

12-02 "Aripiprazole" Presented at Grand Rounds, Arrowhead Regional Medical Center, Colton, CA, 17 Dec 02

12-02 "Treatment Emergent Movement Disorders in Current Clinical Practice" Presented at Grand Rounds, Queens Hospital, Honolulu, HI, 13 Dec 02

12-02 "Advancement in Treatment of Schizophrenia" Presented at Grand Rounds, Tripler VA Army Hospital, Honolulu, HI, 11 Dec 02

11-02 "Evolution of Antipsychotic Therapies: A Pathophysiologic Approach" Presented at National Network if Psychiatric Educators, Laguna Niguel, CA, 15 Nov 02.

10-02 "Side Effects Involving Newer Antipsychotic Medications Including Risk of Cardiovascular Disease and Diabetes" Presented at Grand Rounds, Bakersfield Memorial Hospital, Bakersfield CA, 24 Oct 02.

03-02 "The Atypical Antipsychotic Compounds: What is the Crucial Difference Among Them?" Presented at Psychopharmacology Course, Stanford University, Stanford CA, 9 Mar 02.

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Waco, TX, 7 Mar 02

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Dallas VA Medical Center, Dallas, TX, 7 Mar 02

11-01 "Aripiprazole: Is anything Really New in the Wold of Antipsychotic Medications?" Presented at Abilitat Investigators Meeting, Scottsdale, AZ, 29 Nov 01.

09-01 "The Past, Present, and (Near) Future of Antipsychotic Medications: The Under-appreciated Role of Luck!" Presented at The Annual Meeting of the Northern California Psychiatric Society, Saratoga, CA, 19 Sep 01.

07-01 "The Metabolic Side Effects of the Newer Antipsychotic Compounds: The TD of the New Millennium." Presented at Grand Rounds, UC Irvine, Irvine, CA, 17 Jul 01.

05-01 "The Toxicities of the So-Called 'Atypical Antipsychotics'--Focus on Dyslipidemia." Presented at Grand Rounds, Utah Neuropsychiatric Institute, Salt Lake City, Utah, 22 May 01.

04-01 "Prodromal Phase of Schizophrenia: Diagnosis and Treatment." Presented at W. Covina Mental Health Office, W. Covina, CA, 19 April 01.

03-01 "Risperidone: A Clinical Research Update." Presented at Le Royal Meridien, Toronto, Ontario, Canada, 31 Mar 01.

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Tennessee, Memphis, TN, 9 Feb 01

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Arkansas for Medical Science, Little Rock, AR, 8 Feb 01

02-01 "Use of Antipsychotic Drugs on Treatment Approach for Drug Induced Psychosis." Presented at San Quentin State Prison, San Quentin, CA, 21 Feb 01.

01-01 "EPA and TD with Novel Antipsychotics." Presented at Lanterman State Hospital, Pomona, CA, 25 Jan 01.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at VA Hospital, Seattle, WA, 15 Dec 00.

12-00 "Efficacy and Safety Data of the Atypical Antipsychotics." Presented at Atascadero State Hospital, Atascadero, CA, 14 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, VA Hospital Outpatient Clinic, Roseburg, OR, 12 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly" Presented at Grand Rounds, USC Ingleside Hospital, Rosemead, CA, 8 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, University of Southern California, Los Angeles, CA, 6 Dec 00.

11-00 "Safety and Efficacy Among Atypicals; Treatment Refractory Schizophrenia." Presented at Los Angeles County Jail, Los Angeles, CA, 30 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Olive View Hospital, Sylmar, CA, 16 Nov 00.

11-00 "Long-Term Outcomes with Antipsychotic Medications: The limitations of Our Current Technology." Presented at Ziprasidone National Consultants Forum, Scottsdale, AZ, 14 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at USC Ingleside Hospital, Rosemead, CA, 9 Nov 00.

10-00 "Newer Antipsychotics: Approaches to Treatment Refractory Patients." Presented at 2000 MIRECC Retreat, Los Angeles, CA, 25 Oct 00.

10-00 "Weight Gain and Atypical Antipsychotic Medications: The TD of the New Millennium?" Presented at MHC of Greater Manchester, Manchester, NH, 12 Oct 00.

09-00 "Side Effects of Typical and Atypical Antipsychotic Agents." Presented at the UCLA Medical Plaza, Los Angeles, CA, 11 Sep 00.

09-00 "Safety and Efficacy Among Atypicals." Presented at Sacred Heart Hospital, Spokane, WA, 12 Sep 00

09-00 "Safety and Efficacy Among Atypicals." Presented at Skagit Valley Mental Health, Mt. Vernon, WA, 13 Sep 00.

09-00 "Update on Atypical Antipsychotics." Presented at Porterville Developmental Center, Porterville, CA, 14 Sep 00.

07-00 "Schizophrenia: Treatment with Risperdal." Presented at the Office of Mental Health, New Orleans, LA, 25 Jul 00.

07-00 "Atypicals and Treatment Resistant Schizophrenia." Presented at Loma Linda Behavior Medicine Center, Redlands, CA, 21 Jul 00.

06-00 "Movement Disorders." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 16 Jun 00.

06-00 "Tools for Assessing Symptoms: Side Effect Scales." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 17 Jun 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at UC Irvine Medical Neuropsychology Center, Orange, CA, 30 May 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Dave & Buster's, Orange, CA, 24 May 00.

05-00 "The Side Effects of Antipsychotic Compounds." Presented at Kaiser Permanente, Fontana, CA, 17 May 00.

04-00 "Atypical Antipsychotics" Presented at Riverside County Inpatient, Riverside, CA, 27 Apr 00.

03-00 "The Novel Antipsychotics." Presented at Loma Linda University, Loma Linda, CA, 29 Mar 00.

03-00 "The Cardiovascular Liabilities of the Atypical Antipsychotics: The Next 'Big' Thing." Presented at Grand Rounds, University of Hawaii, 24 Mar 00.

03-00 "The New Antipsychotic Compounds Really 'New'?" Presented at Grand Rounds, Contra Costa County Regional Medical Center, Martinez, CA, 14 Mar 00.

03-00 "Treatment Refractory Schizophrenia: Is there a rational approach?" Presented at American Psychiatric Association & Nevada Association of Psychiatric Physicians, Las Vegas, NV, Sat, 4 Mar 00.

02-00 "The Use of Risperidone in Acutely Psychotic Patients." Presented at Italian Society of Psychopathology (V SOPSI Congress), Rome, Italy, 23 Feb 00.

02-00 "The Differential Toxicities Among the Atypical Antipsychotics." Presented at Grand Rounds, Cedars Sinai Medical Center, Los Angeles, CA, 17 Feb 00.

12-99 Visiting Scholar-numerous presentations, Presented at University of Arkansas, Little Rock, AR, 5-8 Dec 99

11-99 "The Novel Antipsychotic Medications." Presented at Anaheim, CA, 12 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at University of Kansas Medical Center, Kansas City, MO, 5 Nov 99.

11-99 "Atypicals Antipsychotics: Efficacy and Side Effects." Presented at The American Restaurant, Kansas City, MO, 4 Nov 99.

11-99 "Side Effects of Antipsychiatric Compounds." Presented at Colmery O'Neil V A M C, Topeka, KS, 4 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at Western Missouri Mental Health South Auditorium, Kansas City, MO, 4 Nov 99.

10-99 "Is Clozaril still relevant?" Presented at Atascadero State Hospital, San Luis Obispo, CA, 14 Oct 99.

10-99 "Interested in Geriatric population & Economics of the drugs." Presented at Grand Rounds, Loma Linda University, Loma Linda, CA, 8 Oct 99.

09-99 "Side Effects of Atypical Antipsychotics: What can we expect in the short and long term?" Presented at Riverside, CA, 30 Sep 99.

09-99 "New Treatment Options in the Acute Management of Psychosis." Presented at New York, NY, 26 Sep 99.

08-99 "How to Choose the Correct Medication Regimen for the Treatment of Psychotic Manifestations." Presented at Lanterman Developmental Center, Pomona, CA, 26 Aug 99.

07-99 "Schizophrenia and Overview Movement Disorders." Presented at UCLA School of Nursing, Westwood, CA, 26 Jul 99.

07-99 "New and Novel Antipsychotics." Presented at Fairview Developmental Center, Costa Mesa, CA, 15 July 99.

06-99 "Schizophrenia-Current and New Treatment Trends." Presented at San Joaquin County Mental Health Services, Sacramento, CA, 24 Jun 99.

05-99 "Research Experience with the Newer Neuroleptics-Grand Rounds." Presented at Kaiser, San Francisco, CA, 25 May 99.

05-99 "New Treatment Options in the Acute Management of Psychosis." Presented at Boston Marriott Long Wharf, Boston, MA, 22 May 99.

05-99 "The Neurophysiology of Schizophrenia: Focus on the action of the Novel Antipsychotics." Presented at Kaiser, Woodland Hills, CA, 12 May 99.

04-99 "The New Generation of Antipsychotic Medications." Presented at Kaiser Sunset Family Practice, Los Angeles, CA, 26 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Leeds, England, United Kingdom, 9 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Southampton, England, United Kingdom, 8 Apr 99.

04-99 "The Neurophysiology of Schizophrenia: Focus on the Action of the Novel Antipsychotics." Presented at The Schizophrenic Patient: Profiles, Diagnosis and Treatment Conference, Loma Linda University, Loma Linda, CA, 7 Apr 99.

03-99 "Pharmacological Bases for the Putative Neurocognitive Enhancing Impact of Atypical Antipsychotic Agents." Presented at Neurocognitive Impairment in Schizophrenic and Alzheimer's Disorders: Therapeutic Approaches Workshop, International Academy for Biomedical and Drug Research, Paris, FR, 12-13 Mar 99.

02-99 "Antipsychotic Toxicity in the Elderly." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Typical and Atypical Neuroleptics: A Geropsychiatric Perspective." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Somatic Treatments of Psychotic Disorders" Given with course entitled "Recovery from Madness", Alex Kopelowicz, MD and Robert Liberman, MD--Course Chairs.

02-99 "The Comparative Toxicities of the New Antipsychotic Medications." Presented at Harbor UCLA, Torrance, CA, 2 Feb 99.

01-99 "The Treatment of Schizophrenia at the Turn of the Millennium: What Have We Learned?" Presented to local lay chapter of the California Alliance for the Mentally Ill, UCLA Medical Plaza, Los Angeles, CA, 14 Jan 99.

01-99 "Treatment Refractory Schizophrenia: The Role of the "New" Antipsychotic Compounds" Presented at Grand Rounds, UCI Medical Center, Irvine, CA, 5 Jan 99.

11-98 "Treatment of Schizophrenia." Presented at Grand Rounds, UC Davis Medical Center, Sacramento, CA, 11 Nov 98.

11-98 "Atypicals and Side Effects." Presented at Sutter Family Practice Residency Program, Sacramento, CA, 11 Nov 98.

11-98 "Treatment of Refractory Patients and Partial Response." Presented at Janssen-Cilag SpA Laboratories, Beerse, Belgium, 6 Nov 98.

10-98 "The Role of Novel Antipsychotics in the Control of the Acute Psychotic Symptoms." Presented at the WPA Symposium, Guadalajara, MX, 30 Oct 98.

10-98 "Efficacy of Risperdal and the Atypical Antipsychotics." Presented at Grand Rounds, Porterville State Hospital, Porterville, CA, 21 Oct 98.

10-98 "Treatment of the Refractory Patient." Presented at the Grand Geneva Resort Symposium, Lake Geneva, IL, 3 Oct 98.

10-98 "Treatment Resistant Schizophrenia" Presented at the APA-IPS Symposium, Los Angeles, CA, 2 Oct 98.

09-98 "Treatment Refractory Schizophrenia." Presented at Grand Rounds, Oregon Health Sciences University Department of Psychiatry, 29 Sep 98.

09-98 "The Second Generation of 'Anti-schizophrenic' Drugs." Presented at the 1998 William Rondeau Memorial Lecture, Oregon Health Sciences University Department of Psychiatry, 28 Sep 98.

09-98 "Movement Disorders in Psychiatry." Presented at VA Hines, IL, 23 Sep 98.

09-98 "The Role of Atypical Antipsychotics." Presented at Napa State Hospital, CA, 19 Sep 98.

09-98 "Atypical Antipsychotics and Schizophrenia." Presented at Grand Rounds, Menlo Park VAMC, Menlo Park, CA, 11 Sep 98.

08-98 "New Treatment Options in Schizophrenia." Presented at ComCare, Phoenix, AZ, 18 Aug 98.

07-98 "Schizophrenia Overview and Movement Disorders." Presented at the Neuropsychiatric Nurse Practitioner Program, UCLA School of Nursing, Los Angeles, CA, 27 Jul 98.

07-98 "New Treatment Interventions for Psychotic Disorders." Presented at San Joaquin County Mental Health Services, Stockton, CA, 16 Jul 98.

07-98 "Strategies for Rapidly Controlling Acute Psychotic Symptoms." Presented at Napa State Hospital, Napa, CA, 3 Jul 98.

06-98 "New Directions in Psychosis." Presented at Grand Rounds, San Francisco General Hospital, San Francisco, CA, 26 Jun 98.

06-98 "The Clinical Choice: Is an Algorithm Possible?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Treatment of Refractory Psychosis: Is There a Rational Approach?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Drug Treatment of Schizophrenia" Presented as course number 63 with faculty S Marder, J Davis, P Janicak, at the 151st APA Annual Meeting in Toronto, Canada, 2 Jun 98.

05-98 "New Atypical Antipsychotics: Similarities and Differences" Presented via satellite program for Indio and Riverside County Mental Health Inpatient Treatment Facility, Riverside, CA, 28 May 98.

05-98 "New Advances in the Treatment of Schizophrenia" Presented by CME, Inc. at Sheraton Gateway, Los Angeles, CA, 17 May 98.

05-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs" Presented at Merritheu Memorial Hospital, Martinez, CA, 12 May 98.

05-98 "Management of Cognitive Disruption in Schizophrenia" Presented at University of Illinois at Chicago Symposium in Bloomingdale, IL, 5 May 98.

05-98 "Neurocognition, Schizophrenia, and the Role of the Novel Antipsychotic Medications" Presented at the Panhellenic Psychiatric Congress, Limnos, Greece, 2 May 98.

04-98 "Neurocognitive and Functional Assessment - Rationale for M100907 Superiority" Presented at second Neuropsychiatry Forum of Hoechst Marion Roussel in Bridgewater, NJ, 24 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Bergen Pines County Hospital, Paramus, NJ, 23 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Rockland Psychiatric Center, Orangeburg, NY, 22 Apr 98.

04-98 "Update on Anti-psychotic Medications." Presented at Alaska Psychiatric Association's 5th Annual Spring Education Meeting, Anchorage, AK, 18 Apr 98.

03-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs." Presented at Washington State Psychiatric Association Spring Meeting in Vancouver, BC, 28 Mar 98.

03-98 "Schizophrenia and Cognitive Function - Approaching the New Millennium" Presented at National Schizophrenia Symposium, Scottsdale, AZ, 27 Mar 98.

03-98 "Challenge: Making the most of Therapy with Atypical Antipsychotics" Presented at Eastern State Mental Hospital, Williamsburg, VA, 20 Mar 98.

03-98 "Past, Present and Future of Antipsychotic Drugs" Presented for the Virginia State Psychiatric Society, Richmond, VA, 21 Mar 98.

03-98 "Pharmacologic Impact on Neurocognitive Deficits in Schizophrenia:" Presented at Grand Round, Long Beach VA Medical Center, 4 Mar 98.

02-98 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates and Pharmacologic Responsivity" Presented at USC School of Medicine Grand Rounds, 10 Feb 98.

02-98 "Biological bases for Schizophrenia" Presented at the seminar course for undergraduates Psychiatry 98P Professional Schools Seminar Program, UCLA, CA, 4 Feb 98.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at V.A.Psychiatry Service Grand Rounds, Minneapolis, MI, 21 Nov 97.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at HCMC Psychiatry Grand Rounds, MI. 21 Nov 97.

11-97 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates, and Pharmacologic Responsivity" Presented at the Atascadero State Hospital, Atascadero, CA, 19 Nov 97.

11-97 "Pharmacologic Approach to Chronic and Treatment Refractory Schizophrenia" Presented at the Vancouver BCPA Conference, in Vancouver, Canada, 15 Nov 97.

11-97 "New Serotonin/Dopamine Antagonist" - Presented for the Loma Linda Psychiatric Residency Program, Loma Linda, CA, 14 Nov 97

11-97 "The Role of New Generation Antipsychotics in Treatment-Resistant Schizophrenia" - Presented in Grand Rounds at The Chicago Medical School Department of Psychiatry and Behavioral Sciences, Chicago, IL, 6 Nov 97.

10-97 "Beyond Conventional Symptoms" - Presented in Riyadh, Saudi Arabia, 20 Oct 97.

10-97 "Neurocognitive Changes in Schizophrenia" Clinical Pertinence and Impact of Pharmacotherapy" - Presented in Grand Rounds at the University of Nebraska Medical Center, Omaha, NE, 15 Oct 97.

09-97 "Treatment Resistance in Psychosis"- Presented at the Annual Meeting of the Huron Valley Medical Center in in Ypsilanti, MI, 24 Sep 97.

09-97 "Toxic Side Effects of Antipsychotic Medications - Focus on Neuromotor Syndromes" Presented at The Fall 1997 Symposium of Charter Behavioral Health Systems of New England, Nashua, New Hampshire, 20 Sep 97.

09-97 "Risperidone: Efficacy Beyond Conventional Symptoms" Presented at the 10th Annual Meeting of European College of Neuropsychopharmacology, Vienna, Austria, 15 Sep 97.

09-97 "Schizophrenia, Neurocognition, and Antipsychotic Meds" Presented in Grand Rounds at Oregon Health Science University, 9 Sep 97.

09-97 "Past, Present and Future of Antipsychotics" Presented at the Mendota Mental Health Institute Conference Center, Madison, WI, 29 Aug 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Midlands, England, 19 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Kilbride, England, 18 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in Aberdeen, Scotland, 17 Jun 97.

06-97 "Antipsychotics: The Evidence from Experience" Presented at the Janssen Research Foundation in Beerse, Belgium, 16 Jun 97.

06-97 "Atypical Neuroleptics: Newer Antipsychotics" Presented at the Northampton VA Medical Center, Northampton, MA, 4 Jun 97.

05-97 "Beyond Conventional Symptoms: Focus on Risperidone" Presented in Grand Rounds at Vanderbilt University Medical Center, Nashville, TN, 27 May 97.

05-97 "Psychopharmacology in the Geriatric Patient: Utility and Limitations" Presented at the California Society of Internal Medicine annual meeting, San Diego, CA, 24 May 97.

05-97 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 54 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 150th APA Annual Meeting, San Diego, CA, 17-22 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Psychiatric Institute, Washington, DC, 16 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Commission on Mental Health, Washington, DC, 15 May 97.

05-97 "Practical Applications in Atypical Antipsychotics: Clients with Movement Disorders" Presented at Cambridge Hospital, Boston, MA, 14 May 97.

05-97 "The Newer Antipsychotics: Differences and Applications" Presented at Butler Hospital, Providence, RI, 13 May 97.

04-97 "Risperidone and Neurocognition". Presented at the Annual Meeting of the Dutch Psychiatric Society, Amsterdam, Netherlands, 18 Apr 97.

04-97 "Clozapine vs. Haloperidol: Drug Intolerance in a Controlled Six Month Trial" Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

04-97 "Antipsychotic Drug Side-Effects: Objective and Subjective". Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

03-97 "An Update on Atypcial Antipsychotics". Presented in Hyannis, MA, 28 Mar 97.

03-97 "An Update on Atypical Antipsychotics". Presented in New Bedford, MA, 27 Mar 97.

03-97 "The Management of Acute Exacerbations in Chronic Schizophrenia". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "Beyond the Conventional Symptoms". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Beijing, China, 17 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Nanjing, China, 15 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Shanghai, China, 14 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Wuhan, China, 12 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Guangzhou, China, 11 Mar 97.

01-97 "Rational Approach to Antipsychotic Medications and Patient Selection". Presented at the Midwinter Program for Psychiatrists, Lake Tahoe, NV, 28 Jan 97.

01-97 "Current Therapy Options: Efficacy and Side Effects". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

01-97 "Issues in Diagnosis of Schizophrenia". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented to the Hawaii Psychiatric Medical Association, Waikiki, HI, 3 Dec 96.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented at Hawaii State Hospital, Kaneohe, HI, 2 Dec 96.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Newcastle, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Glasgow, Scotland.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Birmingham, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Manchester, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Kyoto Prefectural University, Kyoto, Japan.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Hiroshima University, Hiroshima, Japan.

11-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented in Kurashiki (Okayama City), Japan.

08-96 "New Solutions to Treatment Resistant Schizophrenia". Presented at the 10th World Congress of Psychiatry, Madrid, Spain, 23 Aug 96.

07-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, Costa Mesa, CA.

06-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, San Francisco, CA.

06-96 "The New Generation of Antipsychotic Medications: How Are They Different?". A CME presentation, Staunton, VA.

05-96 "Treatment Resistant Schizophrenia" an industry-sponsored symposium presented at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

05-96 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 61 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

03-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "The Natural History of the 'Schizophrenias'". Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "Update on New Antipsychotic Medications". Presented at University of California, Davis, Davis, CA.

03-96 "Special Populations with Psychoses: First Break Patients, Adolescents and Geriatric Patients". A CME presentation, Long Beach, CA.

02-96 "Psychopharmacology in the Elderly: Cognition and Psychosis". Presented at the Area 7 Symposium, Las Vegas, NV.

02-96 "Side Effects of Antipsychotics: Recognition and Treatment". Presented at Grand Rounds, Stanford University Medical Center, Palo Alto, CA.

01-96 "The History and Current Status of Antipsychotic Drug Development". Presented at Grand Rounds, The Palos Verdes Regional Psychiatric Hospital, Tucson, AZ.

01-96 "The Risk Benefit Profiles of the Serotonin-Dopamine Antagonists". Presented at the University of Arizona, Tucson, AZ.

12-95 "Rational Approaches to Antipsychotic Pharmacotherapy". Presented at the Quarterly Meeting of the County of San Diego Mental Health Services, San Diego, CA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, Seattle, WA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, San Francisco, CA.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hirosaki University Department of Neuropsychiatry, Hirosaki University, Hirosaki, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Akita University School of Medicine Department of Psychiatry, Akita University, Akita, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hokkaido University Department of Psychiatry, Hokkaido University, Hokkaido, Japan.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the SinYang Park Hotel, KwangJu, Korea.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the KwangJu Severance Mental Hospital, KwangJu, Korea.

10-95 "Updáte on Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Meeting of the Korean Neuropsychiatric Association at the Seoul Education Culture Center, Seoul, Korea.

09-95 "Pharmacologic Treatment of Depression" presented to the Quarterly Meeting of the Hawaii Psychiatric Association, Honolulu, Hawaii.

09-95 "Anti-psychotic Medications & Patient Selection: Is There a Rational Approach?" presented to the Hawaii Medical Association at the University of Hawaii, Honolulu, Hawaii.

08-95 "Side Effects of Antipsychotic Medications" presented at the Quarterly Meeting of the Memphis Psychiatric Association, Memphis, TN.

07-95 "Polypharmacy: When is it Reasonable?" Grand Rounds, Alameda County Psychiatric Hospital, Alameda, CA.

07-95 "Behavioral Skill Training in Schizophrenia: Utility and Limitation" Grand Rounds, Atascadero State Hospital, Atascadero, CA.

06-95 "Side Effects of Antipsychotic Medications" Grand Rounds, Loma Linda VA Hospital, Loma Linda, CA.

06-95 "The Treatment of Psychosis in the Elderly" Los Encinas Hospital Annual Symposium, Pasadena, CA.

06-95 "Update on the New Antipsychotic Medications" presented to the Annual Meeting of the California Department of Corrections Psychiatrists, Diamond Bar, CA.

05-95 "How to do research without an NIMH grant" presented at the 148th Annual Meeting of the American Psychiatric Association, Miami, FL, 20-25 May 95.

05-95 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 69 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 148th APA Annual Meeting, Miami, FL, 20-25 May 95.

05-95 "Behavioral Skills Training in Chronic Schizophrenia" presented at the Annual Conference of Western Reserve Psychiatric Hospital, Northfield, OH, 5 May 95.

03-95 "Dopaminergic Modulation of Cigarette Smoking" presented at the Society for Research on Nicotine and Tobacco with Murray E Jarvik, MD, PhD and Nicholas H Caskey, PhD, San Diego, CA.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, St. Louis, MO.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, Philadelphia, PA.

02-95 "The Next Generation of Antipsychotic Medications" presented at Grand Rounds, Veterans Affairs Hospital, Tuskegee, AL.

11-94 "Dosing Strategies with Antipsychotic Compounds: Conventional, SDAs, and Atypicals" presented at the Fall Symposium of New Approaches to Treating Schizophrenia, Chicago, IL, 12 Nov 94.

10-94 "Risperidone: Is It Really Different?" presented at the Fall Conference of the California Alliance For the Mentally Ill, San Francisco, CA, 29 Oct 94.

05-94 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 71 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 24 May 94.

05-94 "Dementia and Movement Disorders in the Elderly," presented as Course 6 with Director JL Cummings, and Faculty WE Reichman, D Sultzer, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 20 May 94.

04-94 "Risperidone, is it really different?" presented at a Stanford University sponsored symposium on the treatment of schizophrenia Palo Alto, CA.

03-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Utah State Alliance for the Mentally Ill, Salt Lake City, Utah.

02-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Washington State mental health workers (psychiatrists and pharmacists), Seattle, WA.

01-94 "The Real Cost of Neuroleptic Treatments" presented to the California State Legislature, Sacramento, CA.

01-94 "The Rational Use of Neuroleptics" presented at the annual educational meeting of the Los Angeles Chapter of Family Practioners, Santa Monica, CA.

10-93 "The Therapeutic Window--The Role of Subjective Experiences" presented at the Quarterly Meeting of the Royal College of Psychiatrists in London, England.

05-93 "Optimum Dosing in Maintenance Treatment." Marder SR, Van Putten T, Wirshing WC, Lebell MB, McKenzie J, Johnston-Cronk K, presented at the 146th APA Annual

Meeting, San Francisco, CA, 26 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 238. (No. 87B)

05-93 "Combined Skills Training and Early Intervention." Marder SR, Wirshing WC, Van Putten T, Eckman TA, Liberman RP, presented at the 146th APA Annual Meeting, San Francisco, CA, 24 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 156. (No. 28D)

05-93 "Clinical Use of Neuroleptic Plasma Levels." presented at the 146th APA Annual Meeting, San Francisco, CA, 25 May 93.

05-93 "Dementia and Movement Disorders in the Elderly," presented as Course 2 with Director JL Cummings, and Faculty WE Reichman and myself, at the 146th APA Annual Meeting, San Francisco, CA, 22 May 93.

01-93 "Hyperkinetic Syndromes in the Elderly" presented at the Geriatric Supercourse in Marina del Rey, CA, 20 Jan 93.

11-92 "Clinical Consequences of Akinesia and Akathisia", presented as first author with T Van Putten and SR Marder at the Association of European Psychiatrists Congress, Barcelona, Spain, 5 Nov 92.

10-92 "The New Atypical Antipsychotics", presented to the South Coast Chapter of the Alliance for the Mentally Ill, Torrance, CA.

06-92 "Impact of Public Opinion and News Media on Psychopharmacology in the 1990's", with Louis Jolyon West, MD, at the College of International Neuropsycho-pharmacology Annual Meeting (CINP), 30 Jun 92, Nice, France.

05-92 "Drug-Induced Movement Disorders in the Elderly," presented at the 145th Annual American Psychiatric Association Meeting, Washington, DC.

03-92 "Fluoxetine-Induced Suicidality: Science, Spurious, or Scientology?" presented at the Daniel X. Freedman Journal Club, UCLA.

01-92 "The Placebo-Controlled Treatment of the Schizophrenic Prodrome," Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

01-92 "Management of the Neuroleptic-Intolerant Patient," presented with D Ames and T Van Putten at UCLA Grand Rounds, Los Angeles, CA.

01-92 "Akathisia with the New Atypical Neuroleptics," presented at Psychiatry Grand Rounds, UCLA-Harbor Medical Center, Torrance, CA.

12-91 "Management of Risk of Rèlapse in Schizophrenia," presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico.

10-91 "Extrapyramidal Symptoms and the Atypical Antipsychotics," presented to the Southern . California Chapter of the California Alliance for the Mentally Ill, Los Angeles.

06-91 "Neuroleptic-Induced Extrapyramidal Symptoms," presented at the Southern California Psychiatric Society, West Hollywood, CA.

05-91 "Pharmacokinetics of Long-Acting Neuroleptics," presented with SR Marder, T Van Putten, J Hubbard, M Aravagiri, and KK Midha, at the American Psychiatric Association 144th Annual Meeting, New Orleans, LA.

05-91 "Fluphenazine Dose in Chronic Schizophrenia," presented with SR Marder, T Van Putten, M Lebell, J McKenzie, and K Johnston-Cronk, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

05-91 "Early Prediction of Schizophrenic Relapse," presented with SR Marder, T Van Putten, M Lebell, K Johnston-Cronk, and J Mintz, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

04-91 "Instrumental Quantification of Akathisia," presented with T Van Putten, SR Marder, JL Cummings, G Bartzokis, and MA Lee at the International Congress on Schizophrenia Research, Tucson, AZ.

04-91 "Antipsychotic Drugs of the Future: The Legacy of Clozapine," presented at the Annual Meeting of the Southcoast Alliance for the Mentally Ill, Fountain Valley, CA.

02-91 "Free Radicals, Movements Disorders, and their Possible Interrelationship," presented to the College of Pharmacy, University of Saskatchewan, Saskatoon, Canada.

11-90 "Primary and Secondary Effects of the Neuroleptics: An Historical Perspective." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

11-90 "Antipsychotic Drugs of the Future: The Legacy of Clozapine." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

10-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." 2nd Annual NARSAD Scientific Symposium, Washington, DC.

06-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." Regional Meeting of NARSAD Supporters, Pasadena, CA.

02-90 "Instrumentation of Drug-Induced Movement Disorders." Neurology Grand Rounds, West LA VAMC, Los Angeles, CA.

02-90 "Functional Versus Organic Psychoses." Psychiatry Grand Rounds, UCLA Harbor Medical Center, Torrance.

10-89 "Use of Quantitative Instruments in the Assessment of Neuroleptic-Induced Movement Disorders." Presented to regional representatives of NARSAD.

04-89 "Management of Risk of Relapse in Schizophrenia. "The Annual Spring Scientific Meeting of the Southern California Psychiatric Society, Hollywood, CA.

03-89 "Quantitative Approaches to Drug-Induced Movement Syndromes." Medical Staff of Camarillo State Medical Facility, Camarillo, CA.

01-89 "Social Skills Training in the Chronic Schizophrenic: A Workshop." 2nd Annual Winter Conference of the American Assn. of Community Psychiatrists, Charleston, SC.

11-88 "Instrumentation of Drug-Induced Movement Disorders." Presented to California state legislators, their aides, and advocates of national mental health groups (NAMI and NARSAD).

08-88 "Classical Cases in Schizophrenia", with JA Talbot, MD, Professor and Chair, Department of Psychiatry, University of Maryland. Program produced with an educational grant from Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

08-88 "Drug-Induced Extrapyramidal Syndromes in Psychiatric Patients." Texas State Hospital medical staff, Big Springs, TX.

06-88 "Role of Psychopharmacology in the Treatment of the Chronic Mental Patient." Department of Corrections at the California Medical Facility in Vacaville, CA.

04-88 "Psychosocial Rehabilitative Treatment of the Chronic Schizophrenic Patient." Presented to the staff of the Roseburg VA Medical Center, Roseburg, OR.

03-88 "Behavioral Rehabilitation of the Chronic Mental Patient." Workshop presented at the First Annual Winter Conference of the American Society of Community Psychiatrists, Colorado Springs, CO.

01-88 "Electromechanical Characteristics of Tardive Dyskinesia." The Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

10-87 "Medication/Consent." Symposium with Drs. R Liberman, J Vaccaro, and J Kane, presented at the 1987 Institute on Hospital and Community Psychiatry, Boston, MA.

09-87 "Medication Management and Patient Education." Annual Department of Mental Health Conference at Michigan State University, East Lansing, MI.

05-87 "Quantitative Assessment of Extrapyramidal Symptoms and Involuntary Movement," presented at a symposium on Acute and Chronic Extrapyramidal Symptoms and Tardive Dyskinesia, at the Annual Meeting of the APA, Chicago, IL.

10-86 "The Affective Disorders Spectrum," presented to the Graduate School of Psychology of the California Lutheran College in Thousand Oaks, CA.

04-86 "Unique Issues of Older Adults with Chronic Mental Health Problems, Focus on Schizophrenia." Mental Health and Aging Conference in Los Angeles, CA.

02-86 "The Geriatric Patient with Cardiac and Psychiatric Problems: Pharmacologic Concerns." VA Nursing Service for their Continuing Education Series in Los Angeles, CA.

10-85 "Psychopharmacologic Treatment of the Geriatric Population," presented to the Psychology interns at the VA as part of their Continuing Education Series in Los Angeles, CA.

Publications

Articles

98. Murphy D, Bailey K, Stone M, Wirshing WC. Addictive potential of quetiapine. *Am J Psychiatry.* 2008 Jul;165(7):918.
97. Tabibian JH, Wirshing DA, Pierre JM, Guzik LH, Kisicki MD, Danovich I, Mena SJ, Wirshing WC. Hepatitis B and C among veterans on a psychiatric ward. *Dig Dis Sci.* 2008 Jun;53(6):1693-8.
96. Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry.* 2007 May;68(5):705-10.
95. Buckley PF, Wirshing DA, Buchan P, Pierre JM, Resinck SA, Wirshing WC. Lack of insight in schizophrenia: impact on treatment adherence. CNS Drugs. 2007;21(2):129-41.
94. Wirshing DA, Pierre JM, Wirshing WC, Guzik LH, Resinck SA, Goldstein D, Zorick TS: Community re-entry program training module for schizophrenic inpatients improves treatment outcomes. *Schizophr Res.* 2006 Oct;87(1-3):338-9.
93. Meyer J, Loh C, Leckband SG, Boyd JA, Wirshing WC, Pierre JM, Wirshing DA: Prevalence of the metabolic syndrome in patients with schizophrenia. *Journal of Psychiatric Practice* 2006; 12(1): 6-10
92. Wirshing DA, Smith RA, Erickson ZD, Mena SJ, Wirshing WC: A wellness class for inpatients with psychotic disorders. *Journal of Psychiatric Practice* 2006; 12(1): 24-29
91. Pierre JM, Peloian J, Wirshing DA, Wirshing WC, Marder SM. A placebo controlled trial of modafinil for negative symptoms in schizophrenia. *Schizophrenia Bulletin* 2005; 31:501
90. Pierre JM, Wirshing DA, Wirshing WC, Rivard JM, Marks R, Mendenhall J, Sheppard K, Saunders DG: High-dose quetiapine in treatment refractory schizophrenia. *Schizophrenia Research* 2005, 73(2-3): 373-375
89. Pierre JM, Wirshing DA, Wirshing WC: High-dose antipsychotics: desperation or data-driven? *Current Psych* 2004, 3(8): 31-37.
88. Pierre JM, Shnayder I, Wirshing DA, Wirshing WC: Intranasal quetiapine abuse. *Am J of Psychiatry* 2004, 161(9):1718
87. McGurk SR, Green MF, Wirshing WC, Wirshing DA, Marder SR, Mintz J, Kern R. Antipsychotic and anticholinergic effects on two types of spatial memory in schizophrenia. *Schizophr Res* 2004, Jun 1;68(2-3):225-33.

86. Marder SR, Glyn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, Mintz J, Liberman RP, Blair KE. Maintenance Treatment of Schizophrenia with Risperidone or Haloperidol: Two-Year Outcomes. *American Journal of Psychiatry*, 2003, 160:1405-1412

85. Wirshing DA, Danovitch I, Erhart SM, Pierre JM, Wirshing WC. Practical tips to manage common side effects. *Current Psychiatry*, 2003 2(3): 49-57

84. Pierre JM, Wirshing DA, Wirshing WC: "Iatrogenic malingering" in VA substance abuse treatment. *Psychiatric Services*, 2003, 54(2): 253-4

83. Wirshing DA, Wirshing WC: Aripiprazole: a viewpoint. *CNS Drugs*, 2002,16(11): 779-786

82. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose, and lipid levels. *J Clin Psychiatry 2002*; 63: 856-865

81. Caskey NH, Jarvik ME, Wirshing WC, Madsen DC, Iwamoto-Schaap PN, Eisenberger NI, Huerta L, Terrace SM, Olmstead RE: Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine & Tobacco Research 2002*; 4:259-266

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78. Umbricht D, Wirshing WC, Wirshing DA, McMeniman M, Schooler NR, Marder SR, Kane JM: Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. *J Clin Psychiatry* 2002; 63(5): 420-424

77. Glynn SM, Marder SR, Liberman RP, Blair K, Wirshing WC, Wirshing DA , Ross D, Mintz J: Supplementing clinic-based skills training with manual-based community support sessions: Effects on social adjustment of patients with schizophrenia. *Am J Psychiatry* 2002; 159(5): 829-37.

76. Wirshing DA, Pierre JM, Wirshing WC: Sleep apnea associated with antipsychotic-induced obesity. *J Clin Psychiatry* 2002; 63(4):369-70.

75. Wirshing DA, Boyd JA, Pierre JM, Saunders CS, Wirshing WC, Azizian K, Patel KR, Ashcraft JC, Darmandjian H, Feusner J: Delusions associated with quetiapine-related weight redistribution. *J Clin Psychiatry* 2002; 63(3): 247-248.

74. Furst BA, Champion KM, Pierre JM, Wirshing DA, Wirshing WC: Possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin. *Biological Psychiatry* 2002; 51(3): 264-265.

- Pierre JM, Wirshing DA, Wirshing WC: Reply to: In response to Furst et al, "possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin." *Biological Psychiatry* 2002; 52: 911-915.

73. Marder SR, Aravagiri M, Wirshing WC, Wirshing DA, Lebell M, Mintz J: Fluphenazine plasma level monitoring for patients receiving fluphenazine decanoate. *Schizophrenia Research* 2002; 53 (1-2): 25-30.

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67. Wirshing DA, Boyd J, Pien J, Wirshing WC: Weight gain and atypical antipsychotics. *Essent Psychopharmacol* 2000; 3(4): 17-35.
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William C. Wirshing, M.D. Date

William C. Wirshing, M.D.

Educational and Professional Background

Education
I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectronic systems). During my tenure there, I was elected to membership in the Phi Beta Kappa and Tau Beta Pi honor societies. The former is traditionally reserved only for those pursuing a "liberal" educational experience (e.g., College of Letters and Science) and the latter is the equivalent entity for students in the science-intensive curriculum of the School of Engineering. Although I then began medical school at UCLA almost immediately following my undergraduate studies, my education was interrupted when my youngest brother developed and then succumbed to brain cancer during my first and second years. During several lengthy arranged absences from school in southern California, I assisted my mother in caring for my brother and worked as an engineer in Mountain View (i.e., "Silicon Valley") California through the beginning of my third year at UCLA.

I completed my undergraduate medical schooling ("on time", despite my protracted absences from campus) with a 3.97 GPA and was given the Sandoz award for "Excellence in the Behavioral Sciences" at graduation in 1982. In addition, I was elected to the Alpha Omega Alpha Medical Honor Society at the end of my third year. I remained at UCLA for both my rotating internship during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency training I was the Chief Resident in Geropsychiatry at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia. My mentors were Professors Van Putten, Goldstein, and Marder.

Clinical, Research, and Teaching Background
I remained at both UCLA and the affiliated West Los Angeles Veterans Affairs Medical Center until late in 2006. Over the two decades between 1986 and 2006 though, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. Though I rose through the traditional academic ranks at UCLA and even reached the level of full Professor over five years ahead of "schedule", I never lost my fascination with clinical care and never traded it for more administrative tasks as my career wandered through the decades. Since leaving the traditional ranks of academia, I have been able to continue and even expand my dual interests in clinical work and teaching. Over the last year I have been Vice President in charge of research and continuing medical education for Exodus Inc. in Culver City, CA and also Clinical Director of Exodus Real Recovery in Agoura Hills,

CA. In a typical month, I now see approximately 325 new patients; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students. Over the course of my career, I have taken care of over twenty five thousand patients, the vast majority of which have suffered from one or another psychotic illness.

As is usual among clinical academicians, my patient care tasks and research interests dovetailed consistently and have always taken place in a setting with medical trainees at every level of experience. Teaching these persons over the years has been the third major leg of my vocational life. Unlike most of my academic colleagues, I never thought of these teaching duties as on obligation to be tolerated and where possible shunted to my younger colleagues. In fact, it generally occupied the top spot in my personal emotional ranking of our traditional tasks (i.e., teaching, research, and patient care). My teaching has been honored over the years with several awards from both my students and colleagues, including 2006 when I was again nominated for the Golden Apple Award by the graduating medical school class (the highest teaching accolade in the School of Medicine). I currently give over 125 routine lectures per year at my various work sites.

Within the context of these various positions and responsibilities, I have been able to experience, study, and then teach others about the care of seriously mentally ill patients. While I have been most consistently compelled by and fascinated with the prototypic psychotic illness schizophrenia, persons with bipolar illness (i.e., "manic depressive disorder") have taken up a close second place over the years. Like any academician in my area, I have sought and received grants to continue my studies and have published in the peer reviewed literature (with the substantial aide of my colleagues and assistants—see my attached CV for the details). I believe that I have been fortunate in the extreme to have had these professional opportunities. They have permitted me to live an enviable work life that I was never able to master and was therefore neither predictable nor routine.

Experience With Industry

These sundry positions also brought me into contact with the pharmaceutical industry that coincidentally became increasingly interested in the treatment of psychotic persons at the very onset of my career in the mid 1980's. This time marked the beginning of the second significant epoch of pharmacologic treatment of psychosis (The first one having begun in the early 1950's but which had plateaued by the late 1960's). This period saw the development, testing, and subsequent marketing of what came to be known as the "Second Generation" or "Atypical" antipsychotic compounds. Though not truly revolutionary or even novel per se (see below), they did constitute a significant advance in many, though not all, aspects over the older medications. This mutual interest in the treatment of psychosis allowed me to "test" potential medications in my patients under controlled protocol conditions from the beginning of their development by industry. Although not every medication that we tested over the years survived the gauntlet of clinical testing, we were able to test every medication that did receive the approval to market by the Food and Drug Administration.

The approval process for medications is a lengthy one that has become increasingly burdened by regulation and requirements over the years. As a consequence, it can take years for a given compound to move from first testing in patients to full marketing approval. Among the medications that we tested and studied that went on to receive approval have been risperidone (approval 1994), olanzapine (1996), ziprazadone (2000), aripiprazole (2002), and quetiapine (1997). The early and prolonged nature of this experience allowed us to develop a clinical knowledge of the real world effects of these drugs that was often at the very forefront of the entire field. As is usual with pharmacologic compounds, our novel discoveries and observations generally involved the toxic effects rather than the therapeutic impacts of the drugs.

In the early to mid 1990's we were among the very first to report on the curious metabolic effects. In particular, we noticed that many of our patients gained weight when first begun on these drugs and at a rate that was, on occasion, singular in our experience. We also noted that these patients soon began to suffer the usual downstream consequences of gaining weight (e.g., glucose intolerance, frank diabetes, and even severe hyperglycemia with resultant hyperosmolar coma). As is customary in the academic world, we described our experience in the peer reviewed literature and reported it at any number of scientific meetings. In addition, though, we worked with industry to extend, understand, and hopefully find ways to remediate these various toxicities. The increasingly high economic stakes of the field sometimes lead those in industry to confuse the message and the messenger (at least from my perspective). As a consequence, our relationships would, or at least could, sour and blossom suddenly, depending on the details of our latest report. As one might expect, our observations and conclusions were not infrequently challenged by one company only to be embraced and promoted by its competitor.

I did not have any direct dealings with Imperial Chemical Industries, as Zeneca was called prior to their name change, while they were developing their antipsychotic compound ICI 204636 (quetiapine's "name" prior to its receiving a formal designation by the nomenclature committee). I was, however, very familiar with the published preclinical and clinical literature on the drug in the 1980's and early 1990's. Immediately after launch in the United States in 1997, I began to lecture for the company and started negotiations with them to perform a high dose clinical trial in a subpopulation of persons with schizophrenia whose symptoms were unresponsive to other available antipsychotic compounds. While a variety of regulatory, legal, and logistical impediments conspired to ultimately thwart my hopes for such a trial, our interest in and experience with high dose treatment did result in a single publication (Pierre, et al, 2005). I continued to lecture and provide ad hoc consultation at the company's request (the last time was August of 2008), though the frequency of these interactions has diminished considerably over time. I have, however, kept them apprised of my concerns about and observation of their drug, including this last spring when I sent them a prepublication copy of a letter that was recently published in the American Journal of Psychiatry (Murphy, et al, 2008). Through out this lengthy association, I would characterize our relationship as mutually respectful and professionally cordial. In notable contrast to some of their corporate peers in the pharmaceutical industry, Astra Zeneca never treated

me dismissively or disrespectfully simply because I would describe an observed toxicity or express an unflattering opinion about quetiapine's clinical characteristics.

History of Antipsychotic Drugs

It can, I think, be persuasively argued that the origins of the "modern" biological theories of psychiatry can be traced directly to the serendipitous discovery of antipsychotic medications in the early 1950's. During that epoch, a trio of French physicians (psychiatrists Delay and Deniker and neurosurgeon Henri Laborit) determined that the experimental Rhône-Poulenc compound RP 4609 (i.e., chlorpromazine or "Thorazine") had a singular power to reduce psychotic symptoms in chronically and severely ill patients with schizophrenia. Schizophrenia is the prototypic psychotic illness that consistently afflicts 0.9 percent of the population, is life long and incurable, runs in families, and generally has its origins in late adolescence or early adulthood. It is further the exclusive province of the human animal—even our closest primate relatives do not develop schizophrenia. It would be difficult to overstate the magnitude of this pharmacologic discovery, coming as it did at a time when wet wraps, hydrotherapy, and frontal lobotomies were the only "effective" palliative treatments. The pharmacologic efficacy of chlorpromazine, though, came with an apparently obligatory neurotoxicity that developed after about two weeks of treatment. This neurotoxicity, which came to be called extrapyramidal symptoms or EPS, included parkinsonism (i.e., slowed movements and mentation, a specific tremor, and muscular rigidity), akathisia (i.e., an intensely dsyphoric sense of restlessness), and dystonia (i.e., sustained, uncontrollable, and functionally disruptive muscular contractions). While these acute EPS could be dramatic and overwhelming, they were transitory and would eventually disappear once the offending agent was discontinued. Unfortunately, there also developed a later, sometimes grotesque disorder of excessive motor movement that was termed tardive dyskinesia (literally "late bad movement"). It was eventually observed that this tardive dyskinesia (TD) would accrue with each passing year of cumulative exposure to the medication at a rate of three to five percent of the treated population per annum. More ominous still was the observation that unlike acute EPS, TD proved to be lifelong and irreversible in a large number of those afflicted (circa 50%), even if the causal agent were permanently discontinued. These neurotoxicities were so consistent, predictable, and uniform that they eventually came to be seen as the hallmark of this class of medications which were termed "neuroleptics" (i.e., "to seize the neuron"). In other words, these antipsychotic medications were defined quite literally by the toxicities they produced.

Though these EPS were the clinical bane of antipsychotic compounds, they were a crucially exploitable characteristic for drug developers. Because there is no animal model for schizophrenia per se, it is not possible to screen potential molecular candidates for this property. There are, however, many excellent animal models for EPS and related behavioral toxicities. It was thus possible to search for potential antipsychotic compounds by simply screening for extrapyramidal liability in one or another of these models. It should come as no surprise then that all antipsychotic medications shared the neurotoxic characteristic—it was this toxicity that allowed them to be discovered in the first place. Arvid Carlsson and colleagues detailed the mechanisms that are believed to underlie this duality (i.e., antipsychotic potential and neurotoxic liability) in the early

1960's. In a series of clever animal experiments and brilliant deductions he proposed that antipsychotics exerted both effects by binding to and blocking dopamine receptors (more specifically the D2 receptor subtype) in the brain. It is of historical note that he shared psychiatry's first Nobel Prize for Medicine in 2000 for these discoveries.

As an ultimate consequence of this process, there came to clinical market an array of often times chemically dissimilar compounds that had equipotent antipsychotic efficacy and were uniformly neurotoxic. They did, of course, vary in a number of secondary characteristics (e.g., anticholinergic potency, sedative potential, tendency to induce orthostatic hypotension, etc.), but their primary efficacies and core toxicities were effectively equivalent. It is important to note that these dopamine receptors are important not only in motor control and psychotic symptoms, but they are also crucial in mediating reward learning. Thus, any antipsychotic molecule that blocks these dopamine receptors will attenuate and possibly destroy an animal's (or a person's) ability to normally experience pleasure. In clinical practice these drugs are notoriously dysphorogenic and exceedingly difficult to subjectively tolerate.

The singular exception to these generalizations about antipsychotics is the compound clozapine. This molecule is a modified structural analog of the tricyclic antidepressant imipramine (a revolutionarily useful and powerful antidepressant medication that has no antipsychotic power whatsoever) and was synthesized by Sandoz Pharmaceuticals in 1959. Though its road to market was torturously long and marred by a number of tragically toxic detours, it ultimately proved itself to be a truly different antipsychotic. It was eventually shown that clozapine had greater antipsychotic power than conventional neuroleptics (as the rest of the antipsychotic market came to be named) and at ordinary antipsychotic doses it failed to cause the EPS that characterized its conventional counterparts. Clozapine then became the prototypic "atypical" antipsychotic in that it alone was a non-neuroleptic antipsychotic: a drug capable of separating antipsychotic efficacy from neurotoxic liability. While a number of often clever and sometimes even compelling explanations of how clozapine is able to exert these clinical behaviors have been elaborated, none have to date been proven. In addition, though the group of more recently developed and marketed antipsychotics (i.e., risperidone, olanzapine, quetiapine, aripiprazole, and ziprazidone) have claimed kinship to clozapine by usurping its "atypical" label, none has matched clozapine's antipsychotic power and all are variably more neurotoxic. This is not to say that as a "class" they have failed to improve upon the conventional compounds, but only that they have not succeeded in truly inheriting clozapine's legacy.

Quetiapine's Development

Imperial Chemical Industries first elaborated what they designated ICI 204636 in the early 1980's. It is a structural analog of clozapine and technically considered a dibenzothiazepine. Its receptor (i.e., the proteinaceous components on the lipid neural membranes of the central nervous system [CNS]) binding profile indicates that it has weak and easily reversible affinity for the classic D2 receptor that Carlsson identified in 1963. It also binds with weak to moderate intensity to a wide spectrum of other receptors in the CNS, but in a pattern that is really unlike any other antipsychotic compound,

including clozapine, upon which its structure is based. These other binding characteristics are conceptualized to account for quetiapine's observed clinical effects. In brief, they confer on quetiapine: sedation, low EPS liability, minimal impact on prolactin, orthostatic hypotension (i.e., a fall in blood pressure when standing), anticholinergic toxicity (i.e., constipation, dry mouth, blurred vision, memory disturbances, and tachycardia), and weight gain liability. All of these ultimately observed characteristics would be expected based only on the neuromolecular characteristics of quetiapine.

Though the knowledge of quetiapine's unique receptor binding profile allowed for the easy prediction of its pattern of toxicity in humans, its low and weak affinity at the critical D2 receptor posed a challenge for protocol designers during its early years of clinical testing. For all conventional compounds the appropriate dose to achieve optimal antipsychotic activity is exactly the dose that also begins to produce EPS. With an "atypical" drug though, the appropriate dose would be an unknown amount lower. Thus, an early hurdle for quetiapine was determining just where the optimal antipsychotic dose range was located. Ultimately quetiapine's FDA registration trials involved multiple doses (five) of quetiapine over a ten fold dosing range compared to single dose of the reference conventional neuroleptic haloperidol. Despite the methodologic asymmetry of this design that markedly favored quetiapine, it failed to beat its conventional comparator at any dose. In fact, the haloperidol arm was generally slightly better (though not statistically so) than any of the five doses of quetiapine. This pattern of being marginally equal to or slightly inferior to comparator drugs has been repeated numerous times over the years of testing. When AZ attempted to perform a meta-analysis (i.e., combining multiple trials to achieve greater statistical power in an effort to show a small effect that is not apparent in any single study) on its accrued dataset, they discovered this very pattern. This disappointing result prompted the marketing personnel within AZ to "spin" these conclusions by touting that quetiapine had "unsurpassed efficacy". While technically correct from a statistical point of view because no single study had shown that any conventional comparator was statistically superior to quetiapine, such hype is clearly disingenuous sophistry.

When considered across many trials involving schizophrenic subjects, quetiapine has been demonstrated to be about 10-20 percent less effective than standard doses of conventional medications. This was shown most clearly in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that was reported in late 2005. This NIMH funded trial compared four atypical medications (quetiapine, ziprazidone, risperidone, and olanzapine) to a single typical medication (perphenazine) and involved 1460 subjects treated over an 18-month epoch. The primary outcome variable was "time to discontinuation" of the assigned drug. The results revealed that quetiapine was about 20 percent less effective than the conventional agent perphenazine (4.6 vs. 5.6 months) and about 50 percent less effective than olanzapine (9.2 months).

While these efficacy facts were disappointing and clearly contributed to quetiapine's dismal market share when it was first approved for use in 1997, it also suggested to me a tantalizing possibility. Because conventional antipsychotic medications were all

essentially equi-efficacious and seemed to share a single underlying mechanism of action, any drug that had demonstrably less efficacy might possibly work through a dissimilar mechanism. This possibility was a major motivating factor in my wanting to pursue a higher than standard dose experimental trial with the company after the drug was launched. I continue to believe that quetiapine does, in fact work through largely distinct mechanisms. Unfortunately this distinction translates into slightly less pharmacologic power on average than conventional medications. AZ has "oversold" quetiapine's efficacy in their marketing endeavors for years.

Quetiapine's Toxic Metabolic Profile

The dataset that Zeneca had compiled on quetiapine prior to its launch in 1997 clearly indicated that clinically significant weight gain was a common side effect of quetiapine. The data from Zeneca's Phase II/III trials demonstrated a clear dose related impact on weight that compellingly worsened over time. Using the FDA's definition of clinically pertinent weight gain (i.e., a 7% increase), quetiapine routinely impacted over 25 percent of the treated population (somewhat lower for lower doses of quetiapine and somewhat higher with higher quetiapine doses). The average shift in weight was 6.2 lbs over the first six months of treatment and 11 lbs after six months of treatment. This is approximately halfway between the weight gain induced by risperidone and olanzapine—quetiapine's major competitors at launch. Weight gains of this magnitude are impressively large and impact an amazingly large and consistent percentage of patients. Despite these data, which have been available to the company since before launch, the label for quetiapine has never, even to the present day, "warned" of this predictable and serious toxicity. Instead, the label has merely listed in the adverse experiences section that quetiapine is "sometimes associated with increases in body weight". Further, their marketing materials over the years have consistently touted that quetiapine is "weight neutral". This is palpably inappropriate and inadequate at best and deceptively misleading at worst. It is my opinion that this labeling deficiency rises to the legal definition of gross negligence (i.e., "willful disregard for the safety of others"). It is unconscionable that after more than a decade's time that the warnings section is still silent about the single most prominent serious toxic characteristic of the compound.

There are a number of well-known health consequences to increases in adiposity. Among these are increased risks for glucose intolerance and even frank diabetes, increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). The fact that quetiapine use results in weight gain and therefore causes diabetes in susceptible patients cannot be rationally disputed. This was confirmed by the APA/ADA consensus conference on the metabolic toxicities of the atypical antipsychotics held in 2004. That conference of independent (i.e., non-industry) experts (at which I provided the presentation on the monitoring protocol) concluded that quetiapine use could result in significant weight gain, increased rates of diabetes, and pathologic changes in lipid profiles. Although the current label change implemented in 2007 does direct one to a new section in the adverse events section that documents, to a degree, some of the measured increases in new onset diabetes, it remains inadequate and misleading. Firstly, the "class labeling" warning section on endocrinologic toxicities is

laced with generalities, disclaimers, and distracting verbiage. It fails completely to state the measured increases in new onset diabetes that are specific to quetiapine and that are detailed in the adverse experiences section. Secondly, it fails to make the known connection between increases in adiposity and subsequent changes in glucose regulation. It gives the mistaken impression that the risks of diabetes only apply to a decidedly minor (circa 2-4%) portion of treated patients when, in fact, nearly one third of patients treated with standard doses for as little as a year are at decidedly increased risk of glucose disregulation. The company personnel have opined in depositions that the details of quetiapine's measured risk of diabetes and related endocrinologic disturbances were unknown until the results of these later done studies were completed. Such rhetoric is intellectually and clinically dishonest as it requires one to deny the clinical fact that increases in adiposity that are caused by quetiapine (and were known to the company before launch in 1997) will result in predictable increase in endocrinologic dysfunction. It is axiomatic that increases in obesity will result in subsequent increases in hyperglycemia, frank diabetes, hyperosmolar coma, and even death due to endocrinologic complications. To deny otherwise, as AZ officials continue to do to the present day, is negligently irresponsible.

Additionally, the label is virtually silent (or at least it is decidedly unclear) about quetiapine's ability to induce massive changes in circulating triglycerides and thereby lead to secondary and potentially lethal pancreatitis (i.e., marked inflammation of the pancreatitis). When a person gains significant adiposity, there is a predictable increase in the levels of circulating lipid pools (i.e., triglycerides, VLDL, LDL, etc.) because to body must manage a larger flow of fats from the gut and to and from the tissues. These changes, while potentially of long-term clinical pertinence, are usually of ordinary magnitude. Quetiapine, though, also results in massive acute elevations in triglycerides that can, on occasion, overwhelm the body's fat management system and cause secondary pancreatitis. The precise mechanisms whereby this toxicity is mediated have yet to be elucidated, however, it is likely that interference with one of the early lipid management enzymes in the liver (e.g., lipoprotein lipase A) causes a "backup" of the triglyceride transport vehicle (i.e., chylomicrons) from the gut that leads to the hypertriglyceridemia. This additional metabolic-like toxicity is unrelated to changes in weight, tends to occur during the first several months of treatment, and is markedly more acutely serious than the more pedestrian increases in the sundry lipid pools that predictably follow increases in adiposity. This toxicity has clearly emerged during the post marketing surveillance period, has been reported frequently in the case report literature, and was discussed at length at the consensus conference in 2004.

Addictive Potential

The single most consistent toxic effect of quetiapine is sedation. This property when coupled with quetiapine's low EPS profile has prompted clinicians to use the drug excessively off-label for such conditions as anxiety and insomnia. These characteristics also raise a reasonable concern that quetiapine may have some addictive potential. In fact clinical experience and a number of case reports have suggested that certain patients will abuse, divert for sale, and become physically dependent on quetiapine (Pierre, et al,

2004; Murphy et al, 2008). Despite these facts the label has been virtually silent about this reality.

Off Label Use

Quetiapine has come to dominate the atypical antipsychotic market primarily because it is used excessively off label (current estimates are about two thirds of the prescriptions are off-label). I am of the opinion that primary among the reasons for this disproportionate off label use are the facts that quetiapine is sedating and highly subjectively tolerable and the inaccurate clinical impression that it is also comparatively free of concerning toxicities and devoid of abuse potential. A secondary reason is that quetiapine's share of the on label market is reduced because it is simply not as potent an antipsychotic as other available products. While prescribing a drug for off label use is a common and often clinically reasonable practice, promoting a drug for off label use is illegal. AZ was clearly aware of the excessive off label use of quetiapine over the years. Their officials have stated repeatedly in depositions that AZ endeavored to provide label support of these "passively observed" prescriptive habits by investing heavily in confirmatory studies. Though many such studies were performed, I consider the claim largely dishonest. If true, then it would have been imperative for AZ to study the largest and most excessive off label use, to wit, insomnia. Such a study would have been logistically and economically trivial to perform, at least in comparison to the studies done in mood and psychosis based disorders. There is to date no evidence of any quality that demonstrates that quetiapine decreases sleep latency, increases total sleep time, normalizes sleep architecture, or improves daytime wakefulness. There is, in fact, ample evidence that quetiapine impairs significantly daytime wakefulness. I believe that AZ knew that any real detailed sleep study would ultimately be an indictment of clinical practice and would potentially cut the total use of their product by more than half. It is further my opinion that AZ mischaracterized the true toxic potential of their product and that this behavior has in part prompted clinicians to use their product inappropriately and excessively off label. If clinicians had been aware of the true metabolic toxicities and addictive liabilities of quetiapine then I do not believe that we would have the amount of off label usage we see today. It is my opinion therefore that AZ has been engaged in "indirect" off label marketing. While their behavior may have in fact been technically within the "letter of the law", it was and continues to be irresponsible, improper, and ethically indefensible.

Conclusions/Summary

AZ's marketing of quetiapine has consistently exaggerated the true efficacy of the compound.

AZ has been aware of the true metabolic toxicities of quetiapine since before launch in 1997. Despite this they have engaged in a marketing campaign that has minimized, obfuscated, or frankly denied these metabolic realities. Their product label has been consistently and continuously inadequate in its warnings about the impact on lipid and glucose metabolism, hyperglycemia, and diabetes. Their label continues to be wholly inadequate to the point of being decidedly misleading in its warnings about weight gain.

Additionally, the current label is inadequate regarding quetiapine's ability to markedly disrupt normal lipid metabolism and cause massive hypertriglyceridemia and secondary pancreatitis.

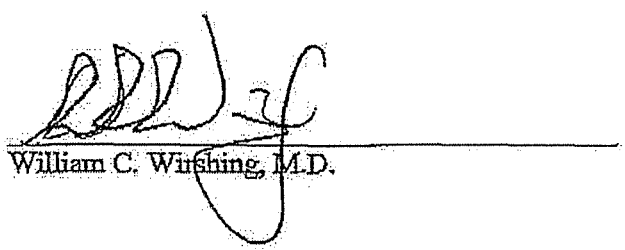
The current label is inadequate in its description about the abuse potential of quetiapine. AZ should have identified and warned of this abuse liability based on the clinical characteristics of quetiapine and the curious and excessive off label use patterns. Further, their tacit acceptance of the excessive use of their product for routine insomnia for the past decade without ever having investigated the effects of their product on sleep, is tantamount to passive marketing for an off label indication. This failure to investigate has been compounded by their insistence that they have behaved responsibly by investing heavily in research to establish on label support for the prescriptive patterns they knew to exist.

AZ's behavior has given prescribing clinicians an inaccurate impression of quetiapine's toxic profile and addictive potential which has robbed physicians of the ability to make informed risk/benefit analysis prior to prescribing quetiapine to a patient. This has led in part to the excessive and inappropriate off label use of the product and to injury and damage to patients who would not have otherwise ever received the medication.

My opinions as stated in this report are based on my education, training, and experience and my review of the relevant literature, internal Astra Zeneca documents, corporate depositions, and public documents and are stated to a reasonable degree of medical probability. It is my understanding that discovery is ongoing and I thus reserve my right to supplement or expound upon my opinions pending review of additional information.

My fees for work in this litigation are $500 per hour.

A list of my testimony for the past 4 years is attached.



William C. Wirshing, M.D.

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prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.

- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it as NOLVADEX may harm your unborn child. Please contact your doctor for birth control recommendations. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX.

What should I avoid or do while taking NOLVADEX?

- You should contact your doctor immediately if you notice any of the following symptoms. Some of these symptoms may suggest that you are experiencing a rare but serious side effect associated with NOLVADEX (see **"What are the possible side effects of NOLVADEX?"**).
  - — new breast lumps
  - — vaginal bleeding
  - — changes in your menstrual cycle
  - — changes in vaginal discharge
  - — pelvic pain or pressure
  - — swelling or tenderness in your calf
  - — unexplained breathlessness (shortness of breath)
  - — sudden chest pain
  - — coughing up blood
  - — changes in your vision

  If you see a health care professional who is new to you (an emergency room doctor, another doctor in the practice), tell him or her that you take NOLVADEX or have previously taken NOLVADEX.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medicines. Be sure to tell your doctor if you are taking warfarin (Coumadin) to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the 2 months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX. Please talk with your doctor about birth control recommendations. If you are taking NOLVADEX to reduce your risk of getting breast cancer, and you are sexually active, NOLVADEX should be started during your menstrual period. If you have irregular periods, you should have a negative pregnancy test before you start NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- If you are taking NOLVADEX to reduce your risk of getting breast cancer, you should know that NOLVADEX does not prevent all breast cancers. While you are taking NOLVADEX and after you stop taking NOLVADEX and in keeping with your doctor's recommendation, you should have annual gynecological check-ups which should include breast exams and mammograms. If breast cancer occurs, there is no guarantee that it will be detected at an early stage. That is why it is important to continue with regular check-ups.

What are the possible side effects of NOLVADEX?

Like many medicines, NOLVADEX causes side effects in most patients. The majority of the side effects seen with NOLVADEX have been mild and do not usually cause breast cancer patients to stop taking the medication. In women with breast cancer, withdrawal from NOLVADEX therapy is about 5%. Approximately 15% of women who took NOLVADEX to reduce the chance of getting breast cancer stopped treatment because of side effects.

The most common side effects reported with NOLVADEX are: hot flashes; vaginal discharge or bleeding; and menstrual irregularities (these side effects may be mild or may be a sign of a more serious side effect). Women may experience hair loss, skin rashes (itching or peeling skin) or headaches; or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough; however, hair loss is uncommon and is usually mild. A rare but serious side effect of NOLVADEX is a blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take NOLVADEX are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if NOLVADEX is stopped. Women may also have complications from treating the clot, such as bleeding from thinning the blood too much. Symptoms of a blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of a blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move to the lungs. If you experience any of these symptoms of a blood clot, contact your doctor immediately.

NOLVADEX increases the chance of having a stroke, which can cause serious medical problems, disability, or death. If you experience any symptoms of stroke, such as weakness, difficulty walking or talking, or numbness, contact your doctor immediately.

NOLVADEX increases the chance of changes occurring in the lining (endometrium) or body of your uterus which can be serious and could include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in the pelvis (lower stomach). These may be caused by changes to the lining (endometrium) or body of your uterus. It is important to bring them to your doctor's attention without delay as they can occasionally indicate the start of something more serious and even life-threatening.

NOLVADEX may cause cataracts or changes to parts of the eye known as the cornea or retina. NOLVADEX can increase the chance of needing cataract surgery, and can cause blood clots in the veins of the eye. NOLVADEX can result in difficulty in distinguishing different colors. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eyes) or hypertriglyceridemia (increased levels of fats in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen). Stop taking NOLVADEX and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking NOLVADEX for a long time.

If you are a woman receiving NOLVADEX for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting NOLVADEX and may be associated with a good response to treatment.

Many of these side effects happen only rarely. However, you should contact your doctor if you think you have any of these or any other problems with your NOLVADEX. Some side effects of NOLVADEX may become apparent soon after starting the drug, but others may first appear at any time during therapy.

This summary does not include all possible side effects with NOLVADEX. It is important to talk to your health care professional about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

How should I store NOLVADEX?

NOLVADEX Tablets should be stored at room temperature (68–77°F). Keep in a well-closed, light-resistant container. Keep out of the reach of children.

Do not take your tablets after the expiration date on the container. Be sure that any discarded tablets are out of the reach of children.

This leaflet provides you with a summary of information about NOLVADEX. Medicines are sometimes prescribed for uses other than those listed. NOLVADEX has been prescribed specifically for you by your doctor. Do not give your medicine to anyone else, even if they have a similar condition because it may harm them.

If you have any questions or concerns, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about NOLVADEX written for health care professionals that you can ask to read. For more information about NOLVADEX or breast cancer, call 1-800-34 LIFE 4.

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Shown in Product Identification Guide, page 306

SEROQUEL®

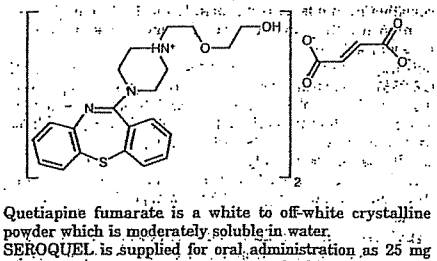
[serō-quēl]

(quetiapine fumarate)

TABLETS

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow), 200 mg (round, white), and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly *via* hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole.

Continued on next page

Seroquel—Cont.

Dose adjustment of quetiapine will be necessary if it is co-administered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**)

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION.**)

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (22/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications).

Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see **Animal Toxicology**). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis.) Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5

day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION.**)

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

Table 1. Treatment-Emergent Adverse Experience Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

Body System/ Preferred Term	SEROQUEL (n=510)	Placebo (n=206)
Body as a Whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous System		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive System		
Constipation	9%	5%
Dry Mouth	7%	3%
Dyspepsia	6%	2%
Cardiovascular System		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and Nutritional Disorders		
Weight gain	2%	0%
Skin and Appendages		
Rash	4%	3%
Respiratory System		
Rhinitis	3%	1%

Continued on next page

Seroquel—Cont.

Special Senses		
Ear pain	1%	0%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

Dose Groups	Placebo	SEROQUEL 75mg	150mg	300mg	600mg	750mg
Parkinsonism EPS	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
incidence	16%	6%	6%	4%	8%	6%
Anticholinergic Medications	14%	11%	10%	8%	12%	11%

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: *Frequent:* hypertonia, dysarthria; *Infrequent:* abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; *Rare:* aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: *Frequent:* flu syndrome; *Infrequent:* neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; *Rare:* abdomen enlarged.

Digestive System: *Frequent:* anorexia; *Infrequent:* increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; *Rare:* glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: *Frequent:* palpitation; *Infrequent:* vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; *Rare:* angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: *Frequent:* pharyngitis, rhinitis, cough increased, dyspnea; *Infrequent:* pneumonia, epistaxis, asthma; *Rare:* hiccup, hyperventilation.

Metabolic and Nutritional System: *Frequent:* peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; *Rare:* glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: *Frequent:* sweating; *Infrequent:* pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; *Rare:* exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; *Rare:* gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; *Rare:* abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: *Frequent:* leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; *Rare:* hemolysis, thrombocytopenia.

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism.

*adjusted for gender

Post Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on

one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

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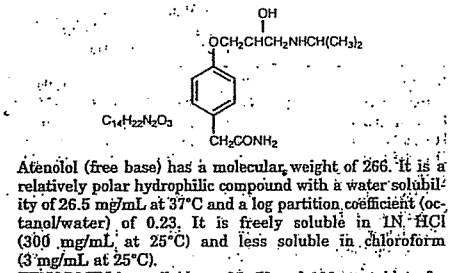
Shown in Product Identification Guide, page 306

TENORMIN® ℞
[ten-or-min]
(atenolol)
ONE TABLET A DAY

DESCRIPTION

TENORMIN® (atenolol), a synthetic, beta$_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. The molecular and structural formulas are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration.

Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

TENORMIN is a beta$_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, TENORMIN inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m^2. (See DOSAGE AND ADMINISTRATION.)

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of TENORMIN, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta$_1$ selectivity of TENORMIN has been shown by its reduced ability to reverse the beta$_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of TENORMIN producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, TENORMIN produced a significantly smaller decrease of FEV$_1$ than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, TENORMIN, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of TENORMIN is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of TENORMIN with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus TENORMIN (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of < 50 bpm or systolic blood pressure < 100 mm Hg, or with other contraindications to beta blockade were excluded. Thirty-eight percent of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the TENORMIN group were to receive TENORMIN I.V. Injection 5-10 mg given over 5 minutes plus TENORMIN Tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either TENORMIN Tablets 100 mg once daily or TENORMIN Tablets 50 mg twice daily on days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first-degree atrioventricular block at entry.

During the treatment period (days 0-7), the vascular mortality rates were 3.89% in the TENORMIN group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the P < 0.05 level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1%-27%. Most of the difference was attributed to mortality in days 0-1 (TENORMIN - 121 deaths; control - 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

Atenolol Geriatric Pharmacology: In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

INDICATIONS AND USAGE

Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

TENORMIN is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending car-

Continued on next page

EXHIBIT 44

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

DECLARATION OF LAURA M. PLUNKETT, Ph.D., DABT

1. My name is Laura M. Plunkett. I am competent to make this declaration, and the facts stated herein are within my personal knowledge and are true and correct.

2. I am a pharmacologist, toxicologist, United States Food and Drug Administration ("FDA") Regulatory Specialist and principal of a consulting company known as Integrative Biostrategies, L.L.C. Based in Houston, Texas, Integrative Biostrategies is a consulting firm that works at the interface of biological science, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

3. I am board certified as a Diplomat of the American Board of Toxicology. I am a member of several professional organizations and have authored or coauthored numerous scientific publications. I have over 20 years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

4. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

5. From June 1984 through August 1986 I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory at the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

6. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduates students in pharmacology and toxicology as well as the neurosciences. During this time I studied drugs of all classes that affect brain function, including antipsychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions.

7. From December of 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically with the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career

(ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on current labeling regulations and generally acted as a regulatory affairs staff for small companies in early stages of product development. A tool common to all my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. I have attached hereto a copy of my curriculum vitae and the expert report I prepared for the Plaintiffs in this litigation, which are attached hereto as Exhibits A and B respectively, and incorporated by reference herein.

8. In my regulatory affairs experience and work with prescription drugs, as well as through my knowledge, skill, training, and experience as a pharmacologist, I am knowledgeable about the "warning" standard established in 21 C.F.R. § 201.57(e). That section requires that drug warnings "shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should have been taken if they occur." Importantly, "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." I am also knowledgeable of the fact that, by law, a prescription

drug "label" includes promotional and marketing materials associated with the drug as well as the "package insert" accompanying the drug's packaging.

9. Based on my knowledge, skill, training, and experience as a pharmacologist and toxicologist and in working with prescription drugs, I am further able to assess the risks associated with a particular drug and, in particular, identify whether the standard "reasonable association of a serious hazard with a drug" is consistent with information related to drug risks and hazards that was known or should have been known by the drug manufacturer. After my review and analysis of AstraZeneca company documents, as well as based on my review of peer-reviewed medical literature pertinent to Seroquel and other antipsychotics, I have formed the following opinions with respect to the adequacy—specifically the accuracy, clarity, and unambiguousness—of Seroquel's labeling from 1999 to present, premised on whether AstraZeneca provided a warning "as soon as there [was] reasonable evidence of an association of a serious hazard" with Seroquel.

10. Regarding the label/package insert accompanying Seroquel from 1999 to the present, studies that I have reviewed reveal that weight gain has long been identified as a serious side effect of anti-psychotic drugs. However, it has also been recognized more recently, according to the pertinent medical literature, that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain. When considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious health effects that pose a risk to a person's health, such as weight gain. Further, my review of AstraZeneca's own documents revealed that the company was aware of the propensity for Seroquel to cause rapid, clinically

significant weight gain. For example, 1997 internal correspondence that I have reviewed show that the company's "Study 15" indicated that weight gain was "rapid," "consistent," "clinically significant," "dose related," and "doesn't stop" during Seroquel treatment. Additionally, by 1999, Dr. Joyce Small, who conducted the company's "Trial 8" for Seroquel, wrote that because the second generation antipsychotics clozapine, olanzapine, and quetiapine "cause the most weight, these drugs may be most likely to induce diabetes." By 2000, AstraZeneca's Global Drug Safety Physician had stated in a company "Safety Position Paper" that there was "reasonable evidence" to suggest that Seroquel "can cause" diabetes, as Dr. Small predicted would result by Seroquel causing clinically significant weight gain. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

11. It is my opinion, therefore, that the 1999-present label/package insert with respect to weight gain is inaccurate, unclear, and ambiguous because the so-called "warning" of weight gain is not contained under the "Warnings" section of the label, but appears much further into the body of the label/package insert in the "Adverse Reactions" section—literally dozens of paragraphs after the "Warnings" section, which is near the top of the label. The weight gain information also fails to describe any of the serious, potentially life threatening side effects associated with weight gain—namely diabetes mellitus and hyperglycemia—of which AstraZeneca was aware. Because there existed reasonable evidence of an association with Seroquel and weight gain, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

12. Moreover, the promotional and marketing materials utilized by the company with regard to weight gain also constituted "label" information that were unclear, inaccurate, and ambiguous in part because they directly contradicted the information contained, for example, in the adverse reactions section of the package insert. For example, the materials that I have reviewed, including Dr. Brecher's 2000 article and Dr. Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or that Seroquel had a favorable weight profile. A handout discussing Dr. Reinstein's experiences with Seroquel in his patients, which I have reviewed, suggested that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. AstraZeneca has also repeatedly stated in sponsored literature and marketing material that I reviewed (such as the Nasrallah and Brecher articles) that there is not a dose-dependent relationship between Seroquel and weight gain. I have also reviewed other sales and marketing "messages" or "themes" that were used by AstraZeneca salespersons in direct contact with physicians during this same time period. Those "messages" or "themes" included claims that Seroquel is "weight neutral," or causes "minimal weight gain" or has a "favorable weight profile." The sales messages contradicted what AstraZeneca knew to be true about Seroquel and weight gain, but also ran counter to Seroquel's own Adverse Reactions section of the label/package insert, which showed (and still shows) that 23% of Seroquel users will experience clinically significant weight gain. For those additional reasons, Seroquel's "label" information regarding "weight gain"—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous with respect to warning about weight gain.

13. Regarding the label/package insert accompanying Seroquel from 1999 to 2004 concerning hyperglycemia and diabetes mellitus, studies that I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious metabolic effects that adversely impact health including diabetes and hyperglycemia, effects that can even become life-threatening if not treated. Further, my review of AstraZeneca's own documents reveals that the company was aware of an association with Seroquel and hyperglycemia/diabetes since at least 1999, when Dr. Small recognized after Trial 8 that Seroquel and two other antipsychotic drugs caused the most weight gain and also were likely to cause diabetes. In 2000, as noted above, the company's Global Drug Safety Physician concluded that Seroquel can cause impaired glucose dysregulation including diabetes. In addition, by November 2002, the Japanese government had evidently reached a similar conclusion, requiring that AstraZeneca send a "Dear Doctor" letter to Seroquel prescribers informing them of the increased risk of diabetes and related complications and mandating that (a) Seroquel not be administered to patients with a history of diabetes; (b) patients treated with Seroquel be monitored carefully including measurement of blood glucose levels; and (c) information regarding the severe adverse reactions that may occur, including diabetic ketoacidosis and diabetic coma, must be fully explained to the patient and family. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

14. It is my opinion, therefore, that the 1999-2004 label/package insert with respect to hyperglycemia/diabetes is inaccurate, unclear, and ambiguous because the so-called "warning" of diabetes and hyperglycemia is not contained under the "Warnings"

section of the label, but appears (again) in the "Adverse Reactions" section of the label/package insert. That section mentions the words "diabetes" and "hyperglycemia" once, and classifies those reactions as "infrequent." The diabetes and hyperglycemia risk is also distorted by the fact that "hypoglycemia" and "weight loss" are also listed as infrequently occurring adverse reactions. As the manufacturer of Seroquel, AstraZeneca was under a duty to revise the label as soon as there was reasonable evidence of an association with the serious health hazards of hyperglycemia and diabetes. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia and diabetes, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

15. Moreover, the promotional and marketing materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this period also constitute "label" information that was unclear, inaccurate, and ambiguous because it too downplayed the severity of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, a study by Dr. Reinstein that was shown to, distributed to, and/or discussed with Seroquel prescribers, the integrity of which has since been discredited, implies that Seroquel patients lost weight and their diabetes was cured after taking Seroquel for ten weeks. For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

16. Regarding the label/package insert accompanying Seroquel from 2004 to 2007 concerning hyperglycemia and diabetes mellitus (the so-called "class warning"), studies that

I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel's effect on weight gain and blood glucose levels differed from some other members of the class of second generation anti-psychotics. Further, the class warning does not describe accurately or clearly the rate and severity of hyperglycemia and diabetes risk associated with Seroquel uniquely, as opposed to other second generation anti-psychotics generally. For example, studies and medical literature that I have reviewed indicate that Abilify and Geodon, two of Seroquel's competitors, are not associated with statistically significant weight gain or hyperglycemia/diabetes to the critical degree that Seroquel has such an association.

17. The warning contained on the 2004-2007 label simply states that hyperglycemia and diabetes "has been reported." The warning is also qualified by statements that elevations in the rates of occurrence of hyperglycemia/diabetes in the schizophrenic or general populations may be confounding factors. In addition, AstraZeneca documents that I have reviewed show the company was aware of this risk long before and during this time period. For example, before and during that time, other international regulatory bodies were requiring specific changes to Seroquel's product labeling related to risks of hyperglycemia and diabetes, but not to anti-psychotics generally—*e.g.,* the Japanese "Dear Doctor" letter. Additionally, in 2005, permission to market Seroquel in France was denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia/diabetes, and the company did not revise the label to clearly,

accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

18. Additionally, the marketing and promotional materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this time also constitute "label" information that was unclear, inaccurate, and ambiguous because it minimized the severity and frequency of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, I have reviewed AstraZeneca documents evidencing that the Reinstein study and the Brecher article were still being disseminated during this time period. In 2006, the FDA Division of Drug Marketing, Advertising, and Communications (FDA DDMAC) admonished the company because it had not satisfactorily disclosed information concerning hyperglycemia and diabetes risks—in accord with the then, current "class warning"—causing the FDA DDMAC to determine that the promotional materials were "misleading" and "undermined the warning." For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

19. Regarding the label that now accompanies Seroquel, that label (which was revised in or about October 2007) still fails to accurately, clearly, and unambiguously warn of Seroquel's dangers relative to diabetes. Following the cross-reference contained in the "Warnings" section to the "Adverse Reactions" reactions section, one sees that "diabetes" is never mentioned in the Adverse Reactions section. However, the data contained in that section shows that, in two long-term clinical trials, Seroquel users exhibited diabetes-level

hyperglycemia more than two times as often as subjects taking placebo. The fact that the Warnings section itself does not mention the disturbing rate with which Seroquel is associated with diabetes renders the warning patently unclear, inaccurate, and ambiguous.

20. The shortcomings of the Warnings section are exacerbated by the Adverse Reaction section's characterization of diabetes-level hyperglycemia as merely "hyperglycemia" and "increased blood sugar." (Fasting blood glucose $\geq$ 126/mg/dl or non-fasting blood glucose $\geq$ 200/mg/dl, as identified in the Adverse Reactions section, is diabetes, not merely "hyperglycemia," according to my knowledge, training, and review of the medical literature identified in my report.). Furthermore, I have reviewed an AstraZeneca internal document in which Seroquel's risk of diabetes-level blood glucose dysregulation is characterized as "common." Because there exists reasonable evidence of an association with Seroquel and diabetes, yet the company failed to revise the label to state the risk of "diabetes" rather than simply "hyperglycemia," the company did not revise the label as required, and it is therefore inaccurate, unclear, and ambiguous.

21. I have reviewed June 2008 FDA correspondence to AstraZeneca regarding the 2007 label indicating that the FDA also deems the current label inadequate. The FDA has requested that AstraZeneca modify the information in the Adverse Reactions section to explain potential design limitations in the studies from which the data mentioned in the above paragraph was drawn. The FDA states that the more than two-fold increase in Seroquel patients contracting diabetes over placebo patients in the studies should be clarified by linking the same to "[t]he mean change in glucose from baseline," which "was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo," a more than five-times greater increase. The

FDA also requested that AstraZeneca state that the blood glucose data may be "underestimated" because of the fact that the studies pre-screened participants who could not tolerate Seroquel (including, for example, because of high blood glucose readings) in the open-label phase prior to randomization, effectively dropping those intolerant participants from the studies, and skewing the results in AstraZeneca's favor. After reviewing the current package insert on the Seroquel.com website at the time of executing this Declaration, AstraZeneca has still not adhered to the FDA's request to change the current label as described. For those additional reasons, Seroquel's current label is inadequate because it inaccurately, unclearly, and ambiguously states the risk of diabetes with Seroquel.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 21st day of November, 2008.

Laura M. Plunkett, Ph.D., DABT

CURRICULUM VITAE

Laura M. Plunkett, Ph.D., D.A.B.T

OFFICE ADDRESS 1223 Melford Drive
Houston, TX 77077-1544

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

President. Integrative Biostrategies (IB) LLC, 2001- present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia, College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Diplomate, American Board of Toxicology, 1993 to present.

Registered patent agent, 1999.

PROFESSIONAL MEMBERSHIPS

Member, Society for Toxicology 1992 - present

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Counselor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 - present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 - present

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4. **Plunkett LM.** Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

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UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Producst Liability Litigation
MDL DOCKET NO. 1769
This Document Relates to ALL CASES

EXPERT REPORT OF
Laura M. Plunkett, Ph.D., DABT
September 6, 2008

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral

research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. During this time, I studied drugs of all classes that affect brain function, including anti-psychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions. Much of my focus was on drugs that affect brain function, which includes anti-psychotics.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labelling regulations and generally acted as a regulatory affairs staff for small companies

in their early stages of product development. A tool common to all work my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. Attached here in Appendix A is a copy of my curriculum vitae.

II. Information Reviewed

7. During the course of work on this case, I have reviewed the following materials:

a) scientific literature relating to the pharmacology and toxicology of anti-psychotic drugs in general and quetiapine (Seroquel) in particular;

b) labelling for Seroquel as provided by the Physician's Desk Reference; and

c) regulations of the U.S. Food and Drug Administration (FDA) relating to the development, approval, labelling and marketing of prescription drug products.

III. Summary of Bipolar Disorder and Schizophrenia

8. Schizophrenia is a major mental illness described by the Diagnostic and Statistical Manual of Mental Disorders ("DSM IV") as a psychotic disorder that is a chronic, severe and disabling brain disease. The hallmark of schizophrenia is disordered thought and perception. Typical symptoms include delusions and hallucinations. While most people diagnosed with schizophrenia are not gainfully employed, a substantial minority do have gainful employment.

9. Bipolar disorder is described by the DSM IV as a mood disorder. Bipolar disorder is a major mental illness, the hallmark of which is manic episodes marked by a euphoric, irritable or expansive mood. Patients with bipolar disorder usually also experience major depressive episodes.

IV. Atypical Anti-psychotics

10. The primary class of drugs used to treat symptoms of schizophrenia and bipolar disorder is known as anti-psychotics. Additionally, mood stabilizers or anti-depressants may also be used to treat bipolar disorder.

11. Anti-psychotics fall into two general categories: the newly developed atypical anti-psychotics and the older, conventional or typical anti-psychotics. The term "atypical" is

applied to the newer drugs mainly because of the lower risks of adverse neurological effects known as extrapyramidal effects. As a general rule, because many atypical anti-psychotics (including Seroquel) still have patent protection, generic versions are not available and as such they are more expensive to purchase and, as a result, more profitable to the manufacturer.

12. Conventional, or typical, anti-psychotics as a group include drugs of a number of different chemical classes. These drugs have efficacy to treat both bipolar disorder and schizophrenia but also often exhibit significant side effects, including risk of acute and long-term neurological side effects, including extrapyramidal effects.

13. Atypical anti-psychotic drugs are considered as having less of a risk of producing extrapyramidal side effects, the unwanted neurological effects that are characterized by changes in movement. In fact, the goal of introducing atypical anti-psychotics to the marketplace was to provide an effective treatment that also improved the quality of life of the patient. While the exact mechanisms responsible for the pharmacological differences between typical and atypical anti-psychotics have not yet been clearly defined, differences have been identified in the pattern of brain neurotransmitter receptor systems affected by the various drugs, effects that can be seen in responses elicited in animal models and/or effects that relate to the pharmacological and toxicological responses in humans.

14. Anti-psychotics will only treat the symptoms of schizophrenia and bipolar disorder; there is no "cure" for such disorders. The etiology of schizophrenia and bipolar disorder also remains to be elucidated, although genetics appears to play some role in these disorders.

15. Quetiapine, marketed in the U.S. under the trade name of Seroquel, is a widely prescribed prescription drug product that was approved by the FDA in 1997 for the treatment of schizophrenia. Seroquel was subsequently approved for management of acute manic episodes associated with bipolar disorder in 2004. I believe that Seroquel is also widely prescribed for off-label uses, including the treatment of sleep disorders, control of agitation, anxiety, aggression and behavioural disturbances.

16. The psychotic symptoms treated with atypical anti-psychotic drugs such as Seroquel include disordered thought processes, disorganized and/or irrational behaviour, and degrees of altered mood, from severe agitation to severe withdrawal. Other drugs that have been or are used in the treatment of psychotic disorders include phenothiazines (*e.g.*, chlorpromazine, also known as Thorazine; thioridazine, also known as Mellaril), thioxanthines (*e.g.*, chloprothixene, also known as Taractan; thiothixene, also known as Navane), haloperidol (Haldol), clozapine (Clorazil), aripiprazole (Abilify), loxapine (Loxitane), molindrone (Moban), pimozide (Orap), olanzapine (Zyprexa), riperidone (Risperdal), and ziprasidone (Geodon). The optimum therapy for treating schizophrenia and bipolar disorder is chosen for each patient based on the patient's medical history, including any risks of known side effects of the drug, and the patient's response to the drug in relation to the drug's efficacy and adverse events.

17. The pharmacology of Seroquel and other similar anti-psychotic drugs is described in many textbooks and review articles (*e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* 2006. Brunton, L.L. et al. (eds.), McGraw-Hill: New York, chapter 18). Seroquel produces its therapeutic and adverse effects through its activity on various receptor systems in the brain and throughout the body. Seroquel is known to be an antagonist of D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, H_1, α_1, and α_2 receptors. The efficacy of Seroquel and other atypical anti-psychotic drugs has been linked to dopaminergic and serotonergic system antagonist activity. However, the exact mechanism by which atypical anti-psychotic drugs produce their effects in schizophrenia and bipolar disorders is not known.

V. Seroquel and Associated Health Risks

18. Seroquel is well absorbed following oral administration, with peak concentrations achieved in the blood within 1.5 hours, and an elimination half-life in the range of 6 hours. It is widely distributed in the body and steady state blood levels are achieved within a few days. Following oral administration, Seroquel is extensively metabolized although the major metabolites are not pharmacologically active.

19. Seroquel use has been associated with deaths that have been attributed to severe liver, kidney, and pancreatic damage. Its adverse effects include, but are not limited to,

ketoacidosis, pancreatitis, diabetes mellitus, weight gain, hyperglycemia, blindness, increased thirst, and hypoglycemia. Other serious injuries associated with Seroquel use include: a potentially fatal condition known as neuroleptic malignant syndrome (NMS); tardive dyskinesia, which can cause potentially irreversible, involuntary movements; and other serious health problems associated with the onset of diabetes including heart disease, blindness, coma, seizures and death. These adverse health effects have been reported following both short-term and longer-term use of Seroquel.

20. Some of the adverse health effects associated with Seroquel use have been attributed to activity of the drug on certain receptor systems in the body. For example, orthostatic hypotension seen in some patients administered Seroquel is thought to be attributed to α_1-adrenergic antagonist activity of the drug while somnolence has been attributed to antagonism of histamine type 1 (H_1) receptors by Seroquel.

21. While Seroquel is similar in basic pharmacological profile to other atypical anti-psychotic drugs, including olanzapine and risperidone, the potency of Seroquel as an antagonist at D_2 and 5-HT_{2A} receptors is less than either olanzapine or risperidone. Differences in potency as an antagonist at certain receptor types may explain some of the differences observed among the various atypical anti-psychotics in terms of both efficacy and toxicity.

22. It has been known for decades that many anti-psychotic drugs have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (*e.g.*, Baldessarini, R.J. 1980. Drugs and the treatment of psychiatric disorders. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition.* A.G. Gilman et al. (Eds.), chapter 19, MacMillan Publishing Co.: New York). However, it has been recognized more recently (since about 1999) that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain and changes in glucose metabolism, as well as the onset of diabetes (*e.g.*, Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723; American Diabetes Association et al. 2004. *Diabetes Care* 27:596-601; Allison, D.B. et al. 1999. *Am. J. Psychiatry* 156:1686-1896; Bobes, J. et al. 2003. *Schizophr. Res.* 62:77-88; Wetterling, T. 2001. *Drug Saf.* 24:59-73; Buse, J.B. et al. 2003. *J. Clin. Epidemiol.* 56:164-170). Moreover, it has

now been recognized that clinically significant hyperglycemia and diabetic complications can occur during anti-psychotic treatment both with and without changes in body weight (Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiatry* 59:337-345; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93). Because of the differences apparent among different anti-psychotic agents in terms of risks of diabetes and weight gain, the effects of Seroquel cannot be considered simply a "class" effect for atypical anti-psychotic drugs (Newcomer, J.W. 2005. *CNS Drugs* 19(Suppl. 1):1-93). Different anti-psychotic drugs, including the second generation atypical anti-psychotic agents, have different toxicological profiles.

23. Between January 1997 and July 2002, numerous adverse drug event reports were submitted to the FDA. These reports indicated that patients consuming Seroquel experienced significant adverse health effects, including hyperglycemia, diabetes, exacerbation of pre-existing diabetes, ketoacidosis, and death. These adverse event reports were discussed in an article by Koller *et al.* (2004. *J. Clin. Psychiatry* 65:857-863). The authors concluded that use of Seroiquel may unmask or precipitate hyperglycemia in patients.

24. Case reports linking Seroquel use with hyperglycemia and/or diabetes appeared in the published literature as early as 1999 (*e.g.,* Sobel *et al.* 1999. *J. Clin. Psychiatry* 60:556-557).

25. A large study involving the U.S. Veterans' Administration (Sernyak, M.J. *et al.* 2002. *Am. J. Psychiatry* 159:561-566) was performed in 1999 where records from all patients being treated nationally with anti-psychotics were examined. The authors reported that there was an increased risk of diabetes with exposure to certain anti-psychotic drugs. One of the drugs shown to be associated with an increased risk was Seroquel.

26. At a conference in Europe in 2002, Lambert and colleagues reported the results of a matched case-control study of California Medicaid claims data from 1997 through 2000. They found that there was an increased risk of developing type II diabetes in patients exposed to Seroquel (Lambert *et al.* 2002. *Eur. Neuropsychopharmacol.* 12:S307).

27. In or about August of 2003, a report in the *Wall Street Journal* showed that a study of 19,878 U.S. military veterans between October 1998 and October 2001 indicated that

Seroquel and other members of the new class of anti-psychotic drugs posed a higher risk of diabetes. The article stated that effects were most pronounced with Seroquel.

28. At a conference of the *International Society for Pharmacoepidemiology* held in Philadelphia on August 23 and 24, 2003, study data were reported that showed that patients on Seroquel had 3.34 times as many cases of diabetes as those on older antipsychotic drugs.

29. When considered as a whole in a weight-of-the evidence assessment, the available scientific data indicate that Seroquel can cause physiological effects known to be risk factors for diabetes, including increased body weight and other metabolic effects, and can cause diabetes itself. The scientific data include case reports published on an ongoing basis since 1999 (Sobel, M. et al. 1999. *J. Clin. Psychiatry* 60:556-557; Procshyn, R.M. et al. 2000. *Can. J. Psychiatry* 45:668-669; Wilson, D.R. et al. 2002. *Schizophr. Res.* 59:1-6; Domon, S.E. and C.S. Cargile. 2002. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496; Sneed, K.B. et al. 2003. *J. Am. Board Fam. Pract.* 16:251-254), clinical data (*e.g.*, Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Wirshing, D.A. et al. 2002. *J. Clin. Psychiatry* 63:856-865; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96; the product insert for Seroquel in 2005, *Physician's Desk Reference*, pp. 662-667), a survey of adverse drug reports (Koller, E.A. et al. 2004. *J. Clin. Psychiatry* 65:857-863), epidemiological data assembled since 1999 (Sobel et al. 1999. *J. Clin. Psychiatry* 60:556-557; Sernyak, M.J. et al. 2002. *Am. J. Psychiatry* 159:561-566; Ollendorf, D.A. et al. 2004. *MedGenMed* 6:5; Citrome, L. et al. 2004. *Psychiatr. Serv.* 55:1006-1013; Leslie, D.L. and R.A. Rosenheck. 2004. *Am. J. Psychiatry* 161:1709-1711; Feldman, P.D. et al. 2004. *J. Am. Med. Dir. Assoc.* 5:38-46; Sacchetti, E. et al. 2005. *Int. Clin. Psychopharm.* 20:33-37; Lambert, B.L. et al. 2006. *Am. J. Epidemiol.* 164:672-681; Guo, J.J. et al. 2006. *J. Clin. Psychiatry* 67:1055-1061; Guo, J.J. et al. 2007. *Pharmacotherapy* 27:27-35), and animal data (Cope, M.B. et al. 2005. *Int. J. Obesity* 29:607-614). Each source of information is important in the analysis of the risks associated with

use of Seroquel, and is consistent with accepted methods for establishing causation in a weight-of-the-evidence analysis (Hill, A.B. 1965. *Proc. Royal Soc. Med.* 58:295-300).

30. I believe that the available scientific data demonstrate that Seroquel consumption and use can cause adverse metabolic effects that include, but are not limited to an increased risk of clinically significant body weight gain, hyperglycemia, altered glucose metabolism, and an increased risk of diabetes and diabetes-related complications.

31. It is also important to remember that although clinical trials had been performed with Seroquel as part of the drug development process, such trials are limited in their ability to identify risks associated with drug use by the general population. This is because such drug development clinical trials are performed in either healthy volunteers or in patients that have often been pre-screened for the propensity to develop adverse effects such as hyperglycemia or diabetes, with such patients then usually excluded from studies. It is only after a drug has been placed on the market, and wider exposure is seen, that a true picture of the adverse effects associated with a drug can be observed. As a result, I believe that companies have the duty to carefully monitor their drugs after approval and during marketing for either the existence of new adverse events or a higher than expected incidence of known adverse effects.

32. Scientific studies have established that there are apparent differences among anti-psychotic drugs in terms of risks of diabetes, weight gain and other adverse health effects discussed above. As a result of these differences, and differences in toxicological profiles, I believe that side effects arising through the consumption of Seroquel cannot be described as a "class effect" for all atypical anti-psychotic drugs.

33. Finally, when considering the adverse health effects associated with use of Seroquel, it is important to realize that Seroquel is not unique in terms of its efficacy. Studies have shown that other anti-psychotic drugs have similar effectiveness to Seroquel but have less risk for hyperglycemia, weight gain, metabolic disturbances and diabetes. Therefore, there are safer alternative therapies that could be used that would also provide for effective treatment but with fewer side effects.

34. For example, in the CATIE Schizophrenia Trial, a trial sponsored by the National Institute of Mental Health which is the largest trial conducted to date comparing efficacy and safety of some of the most prescribed anti-psychotic drugs, it was shown that clozapine was more effective than other atypical anti-psychotics (*i.e.*, Seroquel, Zyprexa, Risperdal). Further, when all of the atypical agents studied were examined, including Seroquel, none of the agents was more effective or better tolerated than the typical anti-psychotic, perphenazine (Manschreck, T.C. and R.A. Boshes. 2007. *Harv. Rev. Psychiatry* 15:245-258; Nasrallah, H.A. 2007. *J. Clin. Psychiatry* 68:5-11).

VI. Mechanisms Underlying the Adverse Effects of Seroquel

35. Although the exact molecular mechanisms responsible for the metabolic effects of Seroquel have not been established, there are data that describe the basic mechanisms that lead to the effects of Seroquel on body weight gain and altered glucose metabolism, and eventually diabetes. However, weight gain is not a prerequisite for atypical anti-psychotic drug-induced effects on glucose metabolism and induction of type II diabetes (Newcomer, J.W. 2004. *Clin. Ther.* 26:1936-1946; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93; Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2002. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2001. *Am. J. Med.* 111:716-723; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

36. Clinically significant body weight gain is often seen with administration of Seroquel to patients (Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96). The effects of atypical anti-psychotics on weight gain have been shown to be attributable to both increased caloric intake (increased appetite) and decreased energy expenditure (Gothelf, D. et al. 2002. *Am.*

J. Psychiatry 159:1055-1057; Virkkunen, M. et al. 2002. *Pharmacopsychiatry* 35:124-126). These mechanisms for increased body weight gain are consistent with the fact that Seroquel has effects on neurotransmitter systems in the brain that affect appetite and mood. It is well-established in the medical literature that a clinically significant increase in body weight is a risk factor for diabetes (*e.g.*, Foster, D.W. 1994. Diabetes mellitus. In: *Harrison=s Principles of Internal Medicine, 13th edition.* K.J. Isselbacher et al. (Eds.), chapter 337, McGraw-Hill: New York). Therefore, any effect of Seroquel to increase body weight is a significant risk for the development of diabetes.

37. As discussed above, Seroquel administration to patients has been linked to an increased risk of type II diabetes (see the weight of the evidence discussion above). The mechanisms responsible for development of type II diabetes have been examined in both animals and humans. Type II diabetes is a disorder that is characterized by normal or high levels of insulin in blood at the same time that glucose levels in blood are elevated. The condition is sometimes referred to as insulin resistance. Insulin normally acts to promote transport of glucose across cell membranes (reducing blood glucose levels) and to inhibit lipolysis. Resistance to the activity of insulin leads to hyperlipidemia and eventually to hyperglycemia and even development of diabetes. Although increased weight gain has been discussed as a likely factor in the development of insulin resistance and drug-induced diabetes, there are data that demonstrate Seroquel-induced effects on glucose metabolism and insulin resistance that are independent of weight gain.

38. Observational data has shown that atypical anti-psychotics that are structurally similar to Seroquel (*i.e.*, clozapine and olanzapine) can exert direct effects on glucose-insulin homeostasis by induction of hyperinsulinemia (Melkersson, K.I. et al. 2003. *Psychopharmacology* 170:157-166; Melkersson, K.I. et al. 2000. *J. Clin. Psychiatry* 61:742-749). The increased levels of insulin lead to decreased insulin sensitivity in tissues and could lead to an insulin-resistant state (Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723). *In vitro* data have shown that olanzapine stimulates insulin release from pancreatic islet cells (Melkersson, K. 2004. *Eur. Neuropsychopharmacology* 14:115-119). Regardless of the exact molecular changes that may occur in any one patient treated with Seroquel, these data indicate

that atypical anti-psychotics that are pharmacologically and chemically similar to Seroquel have direct and indirect effects on glucose metabolism that are consistent with the development of insulin resistance, hyperglycemia and potentially type II diabetes. Considered together, the mechanistic data provide evidence for both direct and indirect effects that can lead to disturbances in glucose metabolism and development of type II diabetes. These findings are supported by findings with atypical anti-psychotic drugs, including data specific to Seroquel, that have linked the drugs to induction of diabetes, apart from the induction of weight gain (Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2003. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2004. *J. Clin. Psychiatry* 65:857-863; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

39. The data indicate that administration of Seroquel can cause diabetes and/or the effects on glucose metabolism that can lead to diabetes. The data also indicate that Seroquel poses a greater risk for hyperglycemia and diabetes, both with and without body weight gain, than some other anti-psychotic drugs.

40. Although available studies have focused on the association of type II diabetes with Seroquel treatment, as well as treatment with other atypical anti-psychotic drugs, the toxicity of these drugs, which includes altered glucose metabolism, obesity, and hyperglycemia, would also be significant risk factors for individuals with undiagnosed type I diabetes or a genetic predisposition for type I diabetes. Type I diabetes is characterized by a loss of insulin secretion capacity due to the loss of beta cells in the pancreas. The loss of insulin secretion capacity means that type I diabetics would need to rely on exogenous sources of insulin to control blood glucose levels. Therefore, it is only common sense that any effects of a drug such as Seroquel to affect glucose metabolism or blood glucose levels would be a greater risk for individuals who already are at risk of type I diabetes or who are not yet exhibiting clinical signs and symptoms of type I diabetes.

VII. Warning of Health Risks

41. Despite the findings of the studies discussed above, AstraZeneca failed to warn the FDA, physicians, other health practitioners, and patients of the adverse metabolic effects associated with the consumption of Seroquel at the time these risks were first identified.

42. A review of the most recent product labelling for Seroquel that is available to health professionals demonstrates that, in my opinion, the warnings related to risks of hyperglycemia and diabetes in particular are not adequate to convey the risks posed by Seroquel itself. The discussion of hyperglycemia and diabetes is put forth as an effect of anti-psychotics in general only.

43. At the time that the Seroquel labelling failed to adequately warn physicians of the risks associated with use of the drug, other international regulatory bodies were requiring specific changes to product labelling related to the risks of hyperglycemia and diabetes that were associated with Seroquel, not anti-psychotics in general. For example, in Japan, physicians were being specifically warned to not use Seroquel in patients with a history of diabetes and to monitor patients for development of glucose abnormalities during treatment with Seroquel, regardless of their medical history. Additionally, in 2005 permission to market Seroquel in France had been denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Accordingly, I believe that the physicians in the U.S., and as a result their patients, were not being supplied with adequate risk information related to hyperglycemia and diabetes even though actions had been taken in other countries to warn physicians and patients of these risks.

44. As a result, I believe that the product warnings were wholly inadequate to warn physicians and their patients of the significant adverse metabolic effects associated with the consumption of Seroquel. Nonetheless, Seroquel was marketed heavily as safe and effective for the treatment of bipolar disorder and schizophrenia, promising fewer side effects than other similar treatments including the other atypical anti-psychotics on the market. Further, Seroquel was being prescribed by physicians for treatment of conditions other than bipolar disorder and schizophrenia (off-label use), which use I believe was known by Astra-Zeneca.

VIII. Conclusion

45. In conclusion, based on my training and experience as a pharmacologist, toxicologist, and risk assessor, it is my opinion that Seroquel can cause hyperglycemia and diabetes. The adverse health effects, including these adverse metabolic effects, associated with the consumption and use of Seroquel were predictable based on the known pharmacological profile of the drug and would have been predicted prior to the approval of Seroquel based on the known effects of other structurally similar anti-psychotic drugs. Moreover, the adverse health effects associated with Seroquel consumption and use can be serious, life-threatening conditions and were recognized in the published medical literature soon after the drug was approved. All opinions expressed in this report are based on a reasonable degree of scientific certainty.

IX. Compensation

46. My compensation by plaintiff's attorney in this matter is at the rate of $300.00 per hour for review of documents and materials related to the case and $400.00 per hour for testimony.

X. Previous Testimony

47. A list of my previous testimony for the past four years is included in Appendix B.

I certify that the foregoing statements made by me are true and correct. Executed this 6th day of September 2008 at Houston, Texas.

LISA GONZALES
MY COMMISSION EXPIRES
February 15, 2009

Laura Plunkett, Ph.D., D.A.B.T.

STATE OF TEXAS)

) ss.

COUNTY OF HARRIS

Subscribed and sworn to me

Before this 6th day of Sept. 2008.

Signature of Notary Public

My Commission Expires February 15, 2009

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT for previous 4 years

Year	Case Name	Law Firm Represented
2004	*Freeman v. Bayer* *Caldwell v. Bayer* *January 6, 2004*	Beckenstein & Oxford (Beaumont, TX)
2004	*Nichols v. Bayer* *January 7, 2004*	Hare, Wynn, Newell, & Newton (Birmingham, AL)
2004	*Sheets v. Perrigo* *February, 2004*	Miller & Associates (Richmond, VA)
2004	*Crowson v. Davol, Inc.* *April 6, 2004*	Hicks Thomas & Lilienstern, LLP (Houston, TX)
2004	*McAllister v. Metabolife* *Deposition - April 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Valverde v. Bayer* *May 26, 2004*	Waters & Kraus (Dallas, TX)
2004	*McAllister v. Metabolife* *Trial - June 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Havey v. Wyeth* *Deposition – July 16, 2004*	Waters & Kraus (Dallas, TX)
2004	*Jensen v. Wyeth* *Deposition – August 12, 2004*	Neilsen & Senior (Salt Lake City, UT)
2004	*Thompson v. Wyeth* *Deposition – August 24, 2004*	Williams, Dailey, O'Leary, Craine & Love (Portland, Oregon)
2004	*Havey v. Wyeth* *Trial – September 14, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Valverde v. Bayer Corp* *Trial – September 29, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Berg v. Bayer* *Deposition – October 13, 2004*	Williams Love O'Leary Craine & Powers, P.C. (Portland, OR)

Year	Case Name	Law Firm Represented
2004	*Turney v. Novartis Consumer* *Deposition – October 19, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Spencer v. Duramed* *Deposition – November 9, 2004*	Ashcraft & Gerel (Washington, DC)
2005	*Hawkins v. Metabolife* *Deposition – February 1, 2005*	Simmons-Cooper, L.L.C. (East Alton, IL)
2005	*Spears v. Swift* *Deposition – February 8, 2005*	Johanson & Fairless, LLP (Sugar Land, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – March 1, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Turney v. Novartis* *Trial – March 7, 2005*	Waters & Kraus (Dallas, Texas)
2005	*Kelly Longoria, Douglas Woody v. Metabolife Intl.* *Deposition – March 14, 2005*	Blizzard Law Firm (Houston, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – April 19, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Vogt v. Wyeth* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Crowe v. Perrigo* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Moore v. Wyeth* *Deposition – August 17, 2005*	Abraham Watkins Sorrel & Friend (Houston, TX)
2005	*Sheets v. Perrigo* *Deposition – September 12, 2005*	Miller & Associates (Richmond, VA)
2005	*Blanton* *Deposition – November 11, 2005*	Owens & Fazio (Dallas, TX)
2006	*Geers v. Wyeth* *Trial Testimony – January 23, 2006*	Fleming & Associates (Houston, TX)

Year	Case Name	Law Firm Represented
2006	*Smoot v. AST Sports Science, Inc. et. al.* *Deposition– April 26, 2006*	Ashcraft & Gerel (Alexandria, VA)
2006	*Arrigale/Grossberg v. Merck* *Deposition - June 1, 2006*	Robinson, Calcagnie, & Robinson (California)
2006	*Anderson v. Merck* *Deposition – June 5, 2006*	Abraham Watkins (Houston, TX)
2006	*McNeill v. Ford* *Trial Testimony – June 15, 2006*	Fleming & Associates (Houston, TX)
2006	*Miller v. Merck* *Deposition – June 20, 2006*	Abraham Watkins (Houston, TX)
2006	*Rhone-Poulenc* *Deposition – October 4, 2006*	White and Williams, LLP (Philadelphia, PA)
2007	*Allen* *Deposition – January 25, 2007*	Blizzard Law Firm (Houston, TX)
2007	*Arts Street Fire* *Deposition – February 6, 2007*	The Caluda Law Firm (Metairie, LA)
2007	*Zyprexa MDL 1596* *Deposition – April 25, 2007*	Fibich, Hampton & Leebron (Houston, TX)
2007	*Armendariz* *Deposition – June 13, 2007*	Waters & Kraus (Dallas, TX)
2007	*NJ Education Day* *Testimony – July 24, 2007*	Weitz & Luxembourg (New York, NY)
2008	*Arts Street Fire* *Deposition – February 27, 2008*	The Caluda Law Firm (Metairie, LA)
2008	*Steele v. GSK* *Deposition – July 10, 2008*	Tracey Law Firm (Houston, TX)

EXHIBIT 45

C

Effective:[See Text Amendments] to June 29, 2006

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration, Department of Health and Human Services
Subchapter C. Drugs: General
Part 201. Labeling
Subpart B. Labeling Requirements for Prescription Drugs and/or Insulin

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

<Text of section effective until June 30, 2006.>

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) Description.

(1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for la- bels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) Clinical Pharmacology.

(1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of informa- tion.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) Indications and Usage.

(1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) Contraindications. Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and

Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) Precautions. Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General. This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) Information for patients. This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

(3) Laboratory tests. This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) Drug interactions. This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions. This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility. This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogen-

ic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) Pregnancy. This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) Teratogenic effects. Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy

Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the labeling states: "(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) Nonteratogenic effects. Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery. If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers.

(i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from (name of drug)(or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when (name of drug) is administered to a nursing woman."

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (name of drug)(or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman."

(9) Pediatric use.

(i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized

in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (___) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of

the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

(10) Geriatric use.

(i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the "Geriatric use" subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), ___ percent were 65 and over, while ___ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the "Contraindications," "Warnings," "Dosage and Administration," or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection shall include the statement:

"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal func- tion."

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the "Geriatric use" subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications," "Warnings," or "Precautions" section of the labeling, and the "Geriatric use" subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

"Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely."

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) Adverse Reactions. An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are)(list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) Drug Abuse and Dependence. Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse. This subsection of the labeling shall be based primarily on human data and human experience,

but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence. This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) Overdosage. Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) Dosage and Administration. This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug

incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) How Supplied. This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) Animal Pharmacology and/or Animal Toxicology. In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References". These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

[44 FR 37462, June 26, 1979; 55 FR 11576, March 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998]

SOURCE: 40 FR 13998, March 27, 1975; 51 FR 8182, March 7, 1986; 51 FR 43904, Dec. 5, 1986; 52 FR 2111,

Jan. 20, 1987; 53 FR 4135, Feb. 12, 1988; 54 FR 39635, Sept. 27, 1989, 57 FR 54300, Nov. 18, 1992; 58 FR 45201, Aug. 26, 1993; 62 FR 51515, Oct. 1, 1997; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999, unless otherwise noted.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

LAW REVIEWSA state of extinction: Does Food and Drug Administration approval of a prescription drug label extinguish state claims for inadequate warning? 58 Food & Drug L.J. 287 (2003)."Dot.com medicine"--Labeling in an internet age. 56 Food & Drug L.J. 143 (2001).Is it worth the trouble? The new policy on dissemination of information on off-label drug use under the Food and Drug Administration Modernization Act of 1997. 54 Food & Drug L.J. 645 (1999).Off-label use, prescription, and marketing of FDA-approved drugs: An assessment of legislative and regulatory policy. 51 Fla. L. Rev. 181 (1999).State statutes affecting the labeling of OTC drugs: Constitutionality based on Commerce Clause and federal preemption theories. 46 Food Drug Cosm. L.J. 629 (1991).The learned intermediary doctrine: The correct prescription for drug labeling. 48 Rutgers L. Rev. 821 (1996).The mass marketing of prescription drugs and its effect on the learned intermediary doctrine. 25 Okla. City U. L. Rev. 745 (2000).UNITED STATES CODE ANNOTATEDMisbranded drugs and devices, see21 USCA § 352.21 C. F. R. § 201.57, 21 CFR § 201.57

END OF DOCUMENT

EXHIBIT 46

IN THE UNITED STATES DISTRICT COURT

FOR THE MIDDLE DISTRICT OF FLORIDA

ORLANDO DIVISION

MDL DOCKET NUMBER: 1769

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION

DEPOSITION OF:

DONNA K. ARNETT, M.S.P.H

VOLUME II

**** HIGHLY CONFIDENTIAL ****

S T I P U L A T I O N S

IT IS STIPULATED AND AGREED, by and between the parties through their respective counsel, that the deposition of:

DONNA ARNETT, M.S.P.H.

may be taken before Lisa Bailey, Notary Public, State at Large, at University of Alabama at Birmingham, 1655 University Boulevard, Birmingham, Alabama, on October 7, 2008 commencing at approximately 8:30 a.m.

in Table A2 when you look at diabetes and you look at quetiapine and placebo? And you can use the calculator.

A. So you want the relative risk?

Q. Yes.

A. Can I borrow your pen? The relative risk, also known as the risk ratio, is 2.02.

Q. If you look at page 10 of your report, the top paragraph, you see the FDA analyzed all of Study 126 and 127. Your conclusion at the bottom says, "Not unexpectedly given these differences in glucose and insulin resistance, the risk for diabetes was 2.02"?

A. Yes.

Q. And the source for that is that table, isn't it, Doctor? And by "that table," the table we just marked and you just analyzed, Exhibit 24.

A. Yes.

Q. Now, that's not a relative risk that's based on incidence density, is it?

A. No. It's the number of events.

Q. If you look at incidence density instead of number of events, what is the relative risk when you look at quetiapine versus placebo in Table A2? Did you calculate it, Doctor?

A. I'm still trying to understand where the numbers from this table -- what they actually mean when they say "density."

Q. When you calculate the relative risk in Table A2 of diabetes melitis and you look at incidence density, .4 for quetiapine and .6 for placebo, what is the relative risk, Doctor?

A. For -- this does not make sense to me as an epidemiologist. The rate ratio is almost identical to the incidence -- cumulative incidence ratio. But the incidence density ratio is .46 divided by -- .4 divided by .6.

Q. And what is that?

A Point --

MR. BLIZZARD: Are you just asking for the mathematical calculation?

A. -- 67.

Q. Doctor, the relative risk, if you look at incidence density in Table A2 for diabetes melitis when you look at quetiapine versus placebo, .4 to .6 is a relative risk of .67, correct?

A. Yes.

Q. Now --

A. But it's unusual -- I've never seen in all of my 25 years of epidemiologic experience a

rate ratio and an incidence density ratio come on opposite sides of 1. So there's something I don't understand about their calculation of density. So I can't say with accuracy that that's a correct ratio.

Q. You can't say with accuracy that it's not either --

A. No.

Q. -- because you haven't analyzed it, right?

A. I'd have to see how these are calculated. It's fishy.

Q. The opinion that you gave yesterday that Seroquel is unsafe, do you remember that?

A. Yes.

Q. Your opinion that Seroquel is unsafe, is that -- withdrawn.

Is it your opinion that the chemical composition of Seroquel is defective?

A. I cannot comment with expertise about the chemical composition.

Q. Is there a safer alternative design for Seroquel that you think AstraZeneca should have used?

A. From the totality of the data with

respect to weight and metabolic abnormalities, we've discussed the comparator drug Haloperidol appeared safer with those indices. So I can't comment on what AstraZeneca should have created or in contrast to Seroquel. But there are other alternatives out there that are metabolically safer.

Q. Is it your opinion that, according to you, because Seroquel has a greater weight of -- risk of weight and metabolic abnormalities compared to Haloperidol, that, therefore, Seroquel is unsafe?

A. In the absence of having -- let me rephrase that.

In light of the fact that there were other drugs without those metabolic abnormalities that could be used to treat psychoses, in that respect, Seroquel was unsafe.

Q. You haven't looked at any of the first-generation antipsychotics or second-generation antipsychotics to evaluate them for the risk of metabolic abnormalities, have you, Doctor?

A. With respect to the --

MR. BLIZZARD: Object to the form.

A. -- studies that I've evaluated, yes.

Q. Doctor, I asked you whether or not you've evaluated the risk of -- well, let's stick with Haloperidol, for example.

Do you know for Haloperidol how that compares to Seroquel with respect to the risk of EPS?

A. In the follow-up study from the CATIE trial, it appears to be equivalent.

Q. Is it your testimony that involved Haldol?

A. No.

Q. Let me go back to my original question. Is there a safer alternative design for Seroquel that you claim AstraZeneca should have used?

A. I don't -- I don't have an answer.

Q. Did the vast majority of patients who used Seroquel benefit from it?

A. Could you be more specific by the term "vast"?

Q. Did the majority of the patients who used Seroquel benefit from the medicine, ma'am?

MR. BLIZZARD: Object to the form.

A. In my opinion, no. Because there were such high dropout rates in all of the clinical trials that I reviewed that it would indicate that

the vast majority had no benefit because they dropped out.

Q. Do you know how many patients have used Seroquel since it's been brought to the market in the U.S.?

A. No.

Q. Any idea what percentage of patients who used it think it benefited and helped them?

A. It's irrelevant in the aspect of the question at hand regarding diabetes and metabolic risk. Because in randomized clinical trials where you're using a placebo control, you can evaluate benefit versus harm better than observational studies post marketing.

Q. The FDA had all the information, Doctor, to evaluate the risk of metabolic effects from Seroquel when it approved Seroquel, did it not?

A. I could not find all of the metabolic risks that was in the FDA, so I can't answer for the FDA. I couldn't find it.

Q. Did the FDA conclude that the benefits of Seroquel outweighed the risks when the drug was brought to market?

A. I'll make the assumption that they did. I haven't reviewed their documentation.

Q. Has the FDA repeatedly approved Seroquel as safe and effective and that the benefits outweigh the risks --

MR. BLIZZARD: Object to the form.

Q. -- since it's been brought on the market?

A. As I indicated earlier in my testimony, I haven't extensively evaluated all of the FDA documents with respect to Seroquel.

Q. Do you know that Seroquel has been approved for multiple indications since it's been brought to the market in the United States?

MR. BLIZZARD: Object to the form.

A. Yes.

Q. And on each of those occasions, the FDA concluded the benefits outweighed the risks, correct?

MR. BLIZZARD: Object to the form.

A. I can't define what the FDA decided.

Q. You don't know what it means when the FDA approves a medicine for an indication?

A. Yes.

Q. What does it mean?

A. I'm making an assumption that it means that -- actually, I'm not going to make any

assumptions.

Q. So you don't know?

A. I want to go and review their actual criteria before I answer that question.

Q. As you sit here today, you don't know what it means when the FDA approves a medicine for an indication?

A. All I can do as a scientist is -- am I bothering you by the way I'm answering your question?

Q. No. I'm asking do you know --

A. You're just sighing and rolling your eyes at me.

Q. Doctor, I'm just asking you if you know. You're answering and giving very long-winded answers. And my question is very specific.

MR. BLIZZARD: No, no, no. She was giving an answer. Now you've used the opportunity where she was asking you to please stop rolling your eyes to formulate some new question because you didn't like the answer she was about to give. She's doing a very good job of trying to be responsive to you.

BY MR. GOLDMAN:

Q. Doctor, I'm only rolling my eyes because

EXHIBIT 47

08-I-99343 sh

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation
MDL DOCKET NO. 1769

This document relates to all Group One Trial Cases:

Janice Burns v. AstraZeneca LP, et al. Case No. 6:07-cv-15959
Sandra Carter v. AstraZeneca LP, et al. Case No. 6:07-cv-13234
Connie Curley v. AstraZeneca LP, et al. Case No. 6:07-cv-15701
Linda Guinn v. AstraZeneca LP, et al. Case No. 6:07-cv-10291
David Haller v. AstraZeneca LP, et al. Case No. 6:07-cv-15733
Hope Lorditch v. AstraZeneca LP, et al. Case No. 6:07-cv-12657
Eileen McAlexander v. AstraZeneca LP, et al. Case No. 6:07-cv-10360
Clemmie Middleton v. AstraZeneca LP, et al. Case No. 6:07-cv-10949
Charles Ray v. AstraZeneca LP, et al. Case No. 6:07-cv-11102
William Sarmiento v. AstraZeneca LP, et al. Case No. 6:07-cv-10425
Richard Unger v. AstraZeneca LP, et al. Case No. 6:07-cv-15812
Linda Whittington v. AstraZeneca LP, et al. Case No. 6:07-cv-10475

****

ORAL DEPOSITION OF

LAURA M. PLUNKETT, Ph.D., DABT

October 2, 2008

Volume 1

****

looked at some of the Clozapine data because they were head-to-head data. I also looked at -- now, you're talking about just first generation?

Q. Yeah.

A. Oh, okay. Then haloperidol was the main drug, and then there are a few trials that looked at perphenazine.

Q. Okay. Do you think haloperidol is an effective medication in treating mental illness?

A. Yes.

Q. Would you agree with me that first-generation antipsychotic drugs, as a group, are associated with certain movement disorders?

A. Some of them, yes. And some are worse than others, but, yes. In fact, that's how -- if you read my report, I try to start out with sort of a primer on pharmacology. And Goodman & Gilman teaches that there are -- the reasons the second-generations were developed was to try to improve on that safety profile.

Q. So --

MR. ALLEN: Hold on. Take a little break.

(Recess from 12:26 p.m. to 12:27 p.m.)

Q. (BY MR. BROWN) The -- so, as a group, second-generations were studied and ultimately marketed because they had better side effect profiles with respect to movement disorders, correct?

A. I don't know they were ultimately marketed. But that was one of the impetus, looking for drugs that had less of a propensity to produce some of these movement disorders. But what was interesting is if you look at the labeling for the drugs, that statement is not allowed to be put into the labeling. In other words, I don't believe that the evidence has shown head to head, at least to the sufficiency of the FDA, that any one drug has a specific percent advantage over another.

I would agree with you as a class, in general, when you look at first generation versus second, that as a general rule, you expect the second-generations to have less propensity, but that doesn't mean they have no propensity.

Q. Let me ask this question: Have you -- do you have an opinion with respect to whether haloperidol has a better EPS profile than Seroquel?

A. I haven't formed that opinion. I believe that haloperidol has a propensity to produce it and I believe Seroquel does as well.

Q. In doing a risk-benefit analysis, you have to consider side effects, correct?

A. Yes.

Q. Wouldn't you need to know whether one caused EPS more frequently than the other to actually make that assessment?

A. It depends. If you're doing -- it depends what

you're doing with the risk-benefit assessment. My issue -- and maybe this will help you: When I did the risk-benefit assessment here for Seroquel, I was looking for what were the general -- what were the types of risks that had been associated routinely with Seroquel and what were the benefits that were shown? And then when I'm looking at that drug, I make an assessment based upon whether I think the risks outweigh the benefits.

Now, I'm not saying that the risks outweigh the benefits for this drug such that it should be removed from the market. That's not what I'm saying. I'm saying that when I -- and if you look at what my statement is, I believe there are safer alternatives. I believe that if you look at Seroquel, it should not be a first-line agent necessarily because the metabolic risks of this drug are different from some of the other drugs, and that is above and beyond the neuromuscular risks.

That's not to say that there isn't a patient that Seroquel could be given to safely, and it's possible that it is, but I don't think it should be a first-line treatment.

Q. So, it must be so, based on what you just told me, that you have an understanding of the side effect profile of first-generation antipsychotics, correct?

A. Yes.

Q. And you've researched it in forming your opinions

here today, correct?

A. Yes. In general terms, yes.

Q. And do any of the materials you have brought to the dep today or identified in your report discuss the side effect profiles of first-generation antipsychotics?

A. Many of the published articles talk about that. My textbook talks about that. And then you also even have head-to-head clinical data on Seroquel versus some of these other first-generations that talk about side effect profile. So, absolutely, yes.

Q. And you mentioned that there are safer alternatives to Seroquel, correct?

A. I believe there are, yes.

Q. And what are the safer alternatives to Seroquel?

A. I believe that haloperidol would be a safer alternative to Seroquel. I believe that ziprasidone would be a safer alternative to Seroquel, and possibly -- I can't think of the generic name, but Abilify.

Q. And have you carefully reviewed the side effect profiles for haloperidol?

A. I have reviewed the -- I don't know what you mean by "carefully." I certainly, for my perspective in forming my opinions, have reviewed the side effect profile for haloperidol. And in addition to that -- I'm basing my opinions in part on some of the head-to-head studies that I've provided

here for you in my literature and on those disks.

Q. Okay. Do you know what head-to-head studies you looked at that compared haloperidol to Seroquel?

A. I'd have to go through my pile to tell you. I mean, there -- but it's certainly ones -- some of them are cited in my report and then there's others that are on the PDF files that I've given you. But they wouldn't necessarily be cited as a head-to-head study. I'm just telling you that there are studies that -- I know some of the ones in there have haloperidol versus -- usually versus quetiapine and something else as well.

Q. Does haloperidol cause diabetes?

A. I believe that haloperidol has been shown to have some patients that have shown up with metabolic effects certainly because it can produce some weight gain and some of those things. However, I have not formed an opinion in the same way as I have with Seroquel. I have formed the opinion that I think that Seroquel, Zyprexa, and Risperdal -- and I've been very clear on this in my presentation in the New Jersey Education Day -- appear to have a greater and unique risk over a drug like haloperidol and even over, like, ziprasidone and some of the other second-generation drugs.

Q. Did some of the epi literature you rely on quantify the increased risk of diabetes with haloperidol?

A. I'm sure they did because that was a comparative drug

in some of the epi literature.

Q. Would you agree with me that there are a number of studies that show the risk of diabetes is greater for haloperidol versus Seroquel?

A. I'd have to look at the individual studies to answer that, so I don't want to agree with you or disagree with you. If you want to talk about specific numbers like that, I would want to pull the studies out. And if you want to --

Q. We'll do it today.

A. -- show me one, we can look at it.

Q. Would that surprise you? Based on your opinion, would that surprise you that haloperidol had a greater risk, at least in some epi studies, than Seroquel?

A. Not necessarily surprise me. I'd have to look at the individual study though to interpret the data.

Q. And ziprasidone and Abilify are the other two products you think are safer alternatives?

A. I think they could be. Again, it's a patient-specific decision. But I think that based upon the profile I see, they could be safer alternatives.

Q. And as a non-medical doctor, you're never asked for a particular patient what the best medication is, correct?

A. I'm answering this as a pharmacologist. So, if you ask me as a pharmacologist, based upon the information I see, that's how I answer the question, right. I'm not a physician,

so I don't -- I would not make that decision for an individual patient.

Q. Would you agree with me that all drugs have some risk?

A. Yes. I would say that that's a common -- common thing for anything I can think of. Even water has a risk.

Q. So, no drug's a hundred percent safe, correct?

A. That's right.

Q. All drugs have some level of side effects to varying degrees?

A. Yes, some levels, and they differ in severity and occurrence rates.

Q. Medical doctors consider the risks of a medication when they prescribe it, correct?

A. I assume they do and I would hope they do, and I certainly taught my medical students in pharmacology that they should do that.

Q. So, a medical doctor in his or her office today here in Houston, if they're making a determination about what medication's appropriate -- Seroquel, haloperidol, ziprasidone -- they should be doing -- looking at the side effects and the possible benefits and making a determination based on that with that particular patient?

A. Well, again, I think you'd have to ask a doctor what they do. But I certainly would expect my doctor to be familiar

with the side effect profile, as well as the efficacy profile, for any drug that he was to prescribe or attempt to prescribe for me.

Q. Would you agree with me based on your review of all this literature that mentally ill patients are difficult to treat?

A. What do you mean by "difficult to treat"?

Q. That often doctors -- would you agree with me that doctors often need to try a number of different medications in the schizophrenic population -- let's talk about those folks for one minute -- before they can find one that will work?

A. I'm, again, not a physician. I can only speak from what I have read. And certainly from what I have read, I see that doctors often switch patients from one to another. In other words, there's a discontinuation. Doesn't work, you try a different drug, yeah.

Q. Okay. Turn to Paragraph 16 in your report.

A. 16?

Q. Yeah.

MR. ALLEN: Okay. I didn't understand you. Did you say --

MR. LASKER: 16.

MR. ALLEN: 16? I thought -- I thought somebody said "60." I didn't remember there being that many.

Q. (BY MR. BROWN) Dr. Plunkett, I wanted to look at

Who's Who at AstraZeneca

Witness	Position/Background
Aked, Dominic	Medical Affairs Manager
Arnold, Barry, MD	EU Qualified Person for Pharmacovigilance (January 2006 to present); VP Clinical Drug Safety (July 1999 – May 2006)
Arvanitis, Lisa	Former Seroquel Project Physician
Basma, Alie	Safety surveillance team member
Beamish, Don	Commercial Brand Executive Director
Birkett, Geoffrey	Former Vice-President Global Marketing
Bowen, Rebecca	Marketing
Brecher, Martin, MD, MBA	Former Medical Science Director
Brennan, David	Chief Executive Officer, Chairman of the Senior Executive Team, Former Senior Vice-President for Commercialization and Portfolio Management, and former Chairman of the Operations & Portfolio Management Team
Campbell, Denise	Consumer Brand Director
Daniels, Stephanie	Medical Publications
Davis, Chester	State Government Affairs Director
Dev, Vikram	VP, U.S. Drug Safety (June 2006 to present); Senior Medical Director (1999-2004)
Fors, Susanne	Global Regulatory Affairs Director
Gaskill, James	Director Promotional Regulatory Affairs
Geller, Wayne, MD	Medical Director, Drug Safety and former Global Drug Safety Physician (GDSP) for Seroquel
Giddens, Russell	Head of Global Regulatory Affairs for Seroquel
Goldstein, Jeffrey, Ph.D.	Former Director of Clinical Science
Greenidge, Edmund	Promotional Regulatory Affairs
Haas, Ed	Pharmacologist at AZ
Hamill, Kevin	Brand Manager, HCP Primary Care
Holdsworth, Debbie	Commercial
Jackson, Marianne	National Sales Director
Jones, Martin	Global Product Statistician
Lawrence, Richard	Commercial Strategist
Leong, Ronald	Senior Medical Director
Limp, Gerald	U.S. Regulatory Affairs
Lloyd-Washington, Lisa	Seroquel Brand Director
MacFadden, Wayne	Former Director Clinical Research and U.S. Physician for SSeroquel
McKenna, Kevin	VP, Regulatory Affairs, Neuroscience Therapeutic Area
Melville, Margaret	Senior Global Regulatory Affairs Director
Minnick, Jim	U.S. Public Relations
Meulien, Didier	Psychiatrist on the Seroquel Team
Mullen, Jamie	Senior Director, Clinical Research

Witness	Position/Background
O'Brian, Shawn	Commercial
Oldham, Alex	Global Product Team Director
Owen, Richard	Medical Affairs Manager
Patterson, John	Former Executive Director, AstraZeneca PLC (Jan. 2005 to present); Executive VP, AstraZeneca PLC (Jan. 1999 – Dec. 2004)
Post, Janet	Seroquel Study Physician
Rak, Ihor	Seroquel Team Physician in Neuroscience
Repp, Ed	Seroquel Brand Communication Director
Ruhl, Athena	Seroquel Senior Product Manager
Schwartz, Jack	Executive Director, Seroquel Development
Shaw, Joan	Clinical Project Director for Seroquel
Spiers, Janet	Drug Safety Specialist and Safety Evaluation Review Meeting (SERM) Manager
Travers, John	Psychiatrist
Tumas, John	Chair of Seroquel Publications Team
Warner, Linda	Drug Safety Surveillance Associate Director (August 2004 to present); Drug Safety Surveillance Team Leader (May 2002 – July 2004)
Westhead, Emma	Statistician or medical writer
Williams-Hughes, Celeste	Medical Communications Specialist
Zook, Anthony	President and CEO of AstraZeneca US (2006 to present); Senior VP, Commercial Operations (2001-2006); VP Marketing & Sales (1997-2001)

shall appear in the ''Description'' section of the labeling, whether or not it also appears in a ''Product Title.''

(e) The labeling shall contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

[44 FR 37462, June 26, 1979]

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) *Description.* (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) *Clinical Pharmacology.* (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement ''The following in vitro data are available but their clinical significance is unknown.''

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) *Indications and Usage.* (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g.,

chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjuction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the ''Dosage and Administration'' section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) *Contraindications.* Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state ''None known.''

(e) *Warnings.* Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the ''Indications and Usage'' section of the

labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the ''Adverse Reactions'' section of the labeling.

(f) *Precautions.* Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) *General.* This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) *Information for patients.* This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the ''Precautions'' section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

(3) *Laboratory tests.* This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) *Drug interactions.* This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the ''Dosage and Administration'' section of the labeling rather than under this subsection of the labeling.

(ii) *Drug/laboratory test interactions.* This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) *Carcinogenesis, mutagenesis, impairment of fertility.* This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the

significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the ''Warnings'' section of the labeling. Also, under ''Precautions,'' the labeling shall state: ''See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility.''

(6) *Pregnancy.* This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(*a*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ''Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: ''Reproduction studies have been performed in (*kinds of animal*(*s*)) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*).'' The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*b*) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: ''Pregnancy Category B. Reproduction studies have been performed in (*kind*(*s*) *of animal*(*s*)) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.'' If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ''Pregnancy Category B. Reproduction studies in (*kind*(*s*) *of animal*(*s*)) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*c*) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: ''Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to

have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'' The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: ''Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed.'' The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*d*) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: ''Pregnancy Category D. See 'Warnings' section.'' Under the ''Warnings'' section, the labeling states: ''(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.''

(*e*) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: ''Pregnancy Category X. See 'Contraindications' section.'' Under ''Contraindications,'' the labeling shall state: ''*(Name of drug)* may (*can*) cause fetal harm when administered to a pregnant woman. *(Describe the human data and any pertinant animal data.) (Name of drug)* is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.''

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) *Labor and delivery.* If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) *Nursing mothers.* (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: ''Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ''Caution should be exercised when (*name of drug*) is administered to a nursing woman.''

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a nursing woman.''

(9) *Pediatric use.* (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the ''Indications and Usage'' section of the labeling, and appropriate pediatric dosage information shall be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or ''Clinical Studies'' section. As appropriate, this information shall also be contained in the ''Contraindications,'' ''Warnings,'' and elsewhere in the ''Precautions'' sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the ''Pediatric use'' subsection of the labeling and discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' and ''Clinical Studies'' sections. Appropriate pediatric dosage shall be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the

''Contraindications,'' ''Warnings,'' and elsewhere in the ''Precautions'' sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ''Pediatric use'' subsection of the labeling shall contain either the following statement, or a reasonable alternative: ''The safety and effectiveness of (*drug name*) have been established in the age groups __ to __ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).'' Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or the ''Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ''Clinical Pharmacology'' section. Pediatric dosing instructions shall be included in the ''Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the ''Pediatric use'' subsection and, as appropriate, in the ''Contraindications,'' ''Warnings,'' ''Precautions,'' and ''Dosage and Administration'' sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the ''Pediatric use'' subsection of the labeling shall contain an appropriate statement such as ''Safety and effectiveness in pediatric patients below the age of (__) have not been established.'' If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications'' or ''Warnings'' section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: ''Safety and effectiveness in pediatric patients have not been established.'' If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications'' or ''Warnings'' section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA

may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the ''Contraindications,'' ''Warnings,'' or ''Precautions'' section.

(10) *Geriatric use.* (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the ''Indications and Usage'' section of the labeling, and appropriate geriatric dosage shall be stated under the ''Dosage and Administration'' section of the labeling. The ''Geriatric use'' subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the ''Geriatric use'' subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under ''Clinical Pharmacology'' or the ''Clinical Studies'' section. As appropriate, this information shall also be contained in ''Contraindications,'' ''Warnings,'' and elsewhere in ''Precautions.''

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the ''Geriatric use'' subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The ''Geriatric use'' subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection shall include the following statement:

''Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.''

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), __ percent were 65 and over, while __ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified

differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the ''Geriatric use'' subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the ''Contraindications,'' ''Warnings,'' ''Dosage and Administration,'' or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the ''Geriatric use'' subsection of the labeling and in detail under the ''Clinical Pharmacology'' section. The ''Clinical Pharmacology'' section and ''Drug interactions'' subsection of the ''Precautions'' section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the ''Geriatric use'' subsection shall include the statement:

''This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.''

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the ''Geriatric use'' subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications,'' ''Warnings,'' or ''Precautions'' section of the labeling, and the ''Geriatric use'' subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

''Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.''

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) *Adverse Reactions.* An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall

be expressed in rough estimates or orders of magnitude essentially as follows: ''The most frequent adverse reaction(s) to (*name of drug*) is (are) (*list reactions*). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (*list reactions*), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (*list reactions*).'' Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The ''Warnings'' section of the labeling or, if appropriate, the ''Contraindications'' section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) *Drug Abuse and Dependence.* Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) *Controlled Substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) *Abuse.* This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) *Dependence.* This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) *Overdosage.* Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the ''Clinical Pharmacology'' section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) *Dosage and Administration.* This section of the labeling shall state the

recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: ''Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.''

(k) *How Supplied.* This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) *Animal Pharmacology and/or Animal Toxicology.* In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) *''Clinical Studies'' and ''References''.* These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the ''Clinical Studies'' or ''References'' section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks

shall also be identified or discussed in the appropriate section of the labeling for the drug.

[44 FR 37462, June 26, 1979, as amended at 55 FR 11576, Mar. 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998]

§ 201.58 Requests for waiver of requirement for adequate and well-controlled studies to substantiate certain labeling statements.

A request under § 201.57(b)(2)(ii), (c)(2), (c)(3)(i), (c)(3)(v), (f)(9), and (g)(4) for a waiver of the requirements of § 314.126(b) of this chapter shall be submitted in writing as provided in § 314.126(b) to the Director, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or, if applicable, the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. The waiver shall be granted or denied in writing by such Director or the Director's designee.

[55 FR 11576, Mar. 29, 1990, as amended at 70 FR 14980, Mar. 24, 2005]

§ 201.59 Effective date of §§ 201.56, 201.57, 201.100(d)(3), and 201.100(e).

(a) On and after December 26, 1979, no person may initially introduce or initially deliver for introduction into interstate commerce any drug to which §§ 201.56, 201.57, 201.100(d)(3) apply unless the drug's labeling complies with the requirements set forth in the regulations, with the following exceptions:

(1) If the drug is a prescription drug that is not a biologic and not subject to section 505 of the act (21 U.S.C. 355), and was not subject to former section 507 of the act (21 U.S.C. 357, repealed 1997), §§ 201.56, 201.57, and 201.100(d)(3) are effective on April 10, 1981.

(2) If the drug is a prescription drug that on December 26, 1979 is (i) a licensed biologic, (ii) a new drug subject to an approved new drug application or abbreviated new drug application under section 505 of the act or (iii) an antibiotic drug subject to an approved antibiotic form, §§ 201.56, 201.57, and 201.100(d)(3) are effective on the date listed below for the class of drugs to which the drug belongs. Dates are also listed below for the submission of supplemental applications, amendments, and license changes.

(3) If the drug is approved after December 26, 1979 but is a duplicate of a drug approved on or before that date (for example, a drug approved under an abbreviated new drug application or an antibiotic form), §§ 201.56, 201.57, and 201.100(d)(3) are effective on the date listed below for the class of drugs to which the drug belongs. Dates are also listed below for the submission of supplemental applications, amendments, and license changes.

Effective	Revised labeling due	Drug class	Mail routing code
		BIOLOGICS	
Nov. 1, 1982	Nov. 1, 1980	Bacterial vaccines and antigens with no U.S. standard of potency.	HFB–240
Do	do	Skin test antigens	HFB–240
Nov. 1, 1982 [1]	Nov. 1,1980 [2]	Bacteral vaccines and toxoids with standards of potency.	HFB–240
Do	do	Viral and rickettsial vaccines	HFB–240
Do	do	Allergenic extracts	HFB–240
Do	do	Blood and blood derivatives	HFB–240
		NEW DRUGS AND ANTIBIOTIC DRUGS	
Nov. 1, 1982	Nov. 1, 1980	Antiarrhythmics	HFD–110
Do	do	Replenishers and regulators of electrolytes and water balance	HFD–110, HFD–510, and HFD–160
Do	do	Anticonvulsants	HFD–120
Do	do	Adrenal corticosteroids	HFD–510 and HFD–150
Do	do	Aminoglycosides	HFD–520
Do	do	Scabicides	Do.
Do	do	Pediculicides	Do.
Do	do	General anesthetics	HFD–160
Dec. 1, 1982	Dec. 1, 1980	Antivirals	HFD–520
Do	do	Dermatologics	Do.
Jan. 1, 1983	Jan. 1, 1981	Glaucoma ophthalmics	HFD–520
Do	do	Topical otics	Do.

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalcyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Patterson
Exhibit No. 8
6.11.08 C. PERKS

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[illegible] age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like?
For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Shold we get together to chat?

Thanks
Lisa

EXHIBIT 7

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	:CASE NO. :6:06-md-01769-ACC-DAB
MDL Docket No. 1769:	

- - -

December 20, 2007
CONFIDENTIAL

- - -

Oral deposition of WAYNE MACFADDEN, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania, beginning at 9:01 a.m., on the above date, before Ann Marie Mitchell, a Federally Approved Certified Realtime Reporter, Registered Diplomate Reporter and Notary Public for the Commonwealth of Pennsylvania.

- - -

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
1650 Market Street
Philadelphia, Pennsylvania 19103
877.370.3377

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MR. FRITCH: David Fritch with Dechert.
MR. LeGOWER: Donald LeGower with Dechert on behalf of AstraZeneca and the witness.
MR. McCONNELL: Stephen McConnell with Dechert LLP representing defendant AstraZeneca and the witness, Dr. Wayne Macfadden.

- - -

EXAMINATION

- - -

BY MR. ALLEN:

Q. Good morning.
A. Hello.
Q. Can you tell the jury your name, please, sir?
A. My name is Wayne Macfadden.
Q. You're a medical doctor?
A. Yes.
Q. Can you tell the jury how you're employed?
A. Currently?

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Q. Yes, sir.
A. I'm employed at Johnson & Johnson.
Q. Johnson & Johnson Pharmaceuticals?
A. Yes.
Q. Is that the distributor of Risperdal?
A. The Johnson & Johnson family of companies manufactures risperidone, yes.
Q. Risperidone is the generic name of Risperdal, the brand name?
A. Yes.
Q. Tell the jury what Risperdal is.
A. Risperdal is a medication in the antipsychotic class. It's approved for the treatment of schizophrenia.
Q. Do you work on Risperdal?
A. I work on a formulation of risperidone.
Q. Tell the jury who your -- how long you've worked at Johnson &

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Johnson, Janssen.
A. Approximately one year.
Q. Can you give us the approximate start date at Janssen & Janssen? Or Johnson & Johnson, which Janssen -- let me ask this question.
Janssen is a division of Johnson & Johnson?
A. Janssen is one of the operating companies within Johnson & Johnson.
Q. How long -- how long have you -- you said that you worked there approximately a year.
Do you recall when you started?
A. I believe it was November of last year.
Q. November of 2006?
A. Yes.
Q. Just for the record, today is December 20, 2007. Correct?
A. Yes.
Q. Prior to the time that you

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worked at Johnson & Johnson -- let me ask this question. You said you worked at Johnson & Johnson.
Do you work for Janssen, the Janssen division?
A. My division is Ortho-McNeil Janssen Scientific Affairs.
Q. Okay. Prior to working at that pharmaceutical company, where did you work?
A. I was employed at AstraZeneca.
Q. When did you leave AstraZeneca?
A. It was the summer of 2006.
Q. What month?
A. It was August or September, I can't -- one of the two.
Q. Okay. So you had approximately two months off before you began to work at Janssen?
A. Yes.
Q. Okay. Were you terminated or fired from AstraZeneca, or did you

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just leave for better opportunities?
A. I resigned from AstraZeneca.
Q. Why did you -- let me ask this.
Was the resignation a voluntary resignation or a suggested resignation?
A. I chose to resign from AstraZeneca.
Q. And when did you make that decision?
A. Either August or September 2006.
Q. Did you give two weeks notice at the time of resignation, or did you resign and then leave on the same day?
A. I resigned and left on the same day.
Q. Thank you, sir.
Dr. Macfadden, you understand you've been sworn to tell the truth, the whole truth and nothing but the truth.

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Do you understand that?
A. I do.
Q. Do you understand that the oath is a serious matter?
A. Yes.
Q. And the oath says the truth and the whole truth.
Do you understand there's a distinction between the truth and the truth and the whole truth? Do you understand there's a distinction?
MR. McCONNELL: Objection to form.
THE WITNESS: Perhaps you should explain.
BY MR. ALLEN:
Q. Well, let me ask this.
What does it mean to you when you've been sworn in to tell the truth and the whole truth? What does that mean to you as a person who took the oath in this case?
MR. McCONNELL: Objection to form.

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THE WITNESS: I swore to tell the truth.
BY MR. ALLEN:
Q. Okay. Have you ever given a deposition or any sworn testimony before?
A. Yes.
Q. And when did that occur?
A. I don't recall the exact date.
Q. How many times have you given a deposition or sworn testimony before?
A. I've given a deposition once.
Q. Prior to today. Correct?
A. Yes.
Q. Other than that one deposition prior to today, have you given any other sworn testimony before?
A. I have, yes.
Q. Where else? You said you gave a deposition?
A. Yes.
Q. What else?

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A. It was a testimony in a case where I was called in as an expert witness.
Q. Any other testimony, sworn testimony, besides the deposition and the testimony in a case?
A. No, not that I recall.
There was one or two times that -- I think it was twice, that I gave a -- testimony as an expert.
Q. In a courtroom?
A. Yes.
Q. Okay. Anything else?
A. No, I don't recall.
Q. Okay. Here's what I've written down based upon your testimony.
You believe you've given a deposition once before, you don't recall the date, and you believe you've given testimony as an expert in two court cases; is that right?
MR. McCONNELL: Objection to form.
THE WITNESS: That's the

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What did you write?
A. It appears to say "52-week comparison in stabilized patients. 75, 300, 600, 12 Haldol. Primary time to WD," withdrawal.
Q. What does all of that mean?
A. It appears to imply a 52-week study in stabilized patients with 75, 300 and 600, and 12 milligrams Haldol.
Q. Did you learn about the weight gain data in -- of consistent weight gain to a medically significant degree when you were looking into study 15?
A. I don't recall being appraised of that, no.
Q. Remember you told me CAFE was one of the main ones you were in charge of, right?
A. I was the AstraZeneca physician assigned to participate in the study meetings that were conducted by the PIs.

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Q. That was a loser for -- CAFE internally at least when you took your notes, CAFE was a loser when compared with Zyprexa and Risperdal, right?
A. My recollection was that the endpoint was a noninferiority design. My recollection was that the various arms were indeed noninferior to each other.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'll tell you what. Help us out with, as opposed to your external communication, what your internal handwritten note says, read it aloud, please.
MR. MCCONNELL: Objection, form.
THE WITNESS: "Loss on PANSS plus versus OLZ" and RAS.
BY MR. ALLEN:
Q. Doesn't that mean Seroquel lost on the endpoints in the study when compared with Zyprexa and Risperdal?

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A. My recollection was that in trying to understand this, is that there may have been numerical difference between the three arms. However, my recollection was that the primary endpoint was achieved.
Q. Your note says Seroquel "loss," right?
A. Yes.
Q. I'm going to ask you a series of questions on that note about -- following your testimony about your handwritten note about Seroquel loss. I'm going to read them. And I just need your answer.
Dr. Macfadden, were there any clinical trials on Seroquel -- let me rephrase the question.
Dr. Macfadden, was there any clinical trial on Seroquel when it was compared with an active comparator, second generation antipsychotic where Seroquel was shown to be superior with statistical significance in efficacy as

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defined by the study's primary endpoint.
A. Excuse me. Could you read that one more time, please?
Q. Yes, sir. Was there any -- are you aware of any clinical -- let me rephrase it.
Are you aware of any AstraZeneca clinical trial on Seroquel comparing Seroquel to another second generation antipsychotic where Seroquel was shown to be superior with statistical significance on efficacy as efficacy was defined by the study's primary endpoint?
A. That's your question to me now? My recollection was that there was not a study in which there was a significantly -- significant advantage in efficacy for Seroquel compared to other atypicals to the best of my recollection.
Q. Thank you, sir.
This question.
Are you aware of any AstraZeneca clinical trial on Seroquel when compared with a first generation

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antipsychotic where Seroquel was shown to be superior to a degree of statistical significance on efficacy as defined by the study's primary endpoint?
A. To the best of my recollection, there was -- I can't recall a study in which Seroquel demonstrated statistically significantly superior efficacy compared to an atypical regarding schizophrenia.
Q. Yes, sir. And I didn't ask about atypical in my question. Now I'm not talking about first generation. You know the difference between first generation antipsychotics and atypical antipsychotics, do you not?
A. Yes.
Q. So, listen to my question. Are you aware of any AstraZeneca clinical trial on Seroquel where it was compared with a first generation antipsychotic where Seroquel was shown to be superior to a degree of statistical significance on efficacy as efficacy was defined by

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the study's primary endpoint?
A. Not to my recollection, no.
Q. Dr. Macfadden, are you aware of any clinical trial on Seroquel with any active comparator where Seroquel was shown to be superior in efficacy to a statistically significant degree on any endpoint?
A. Excuse me. The comparator was which?
Q. Any?
A. I can't immediately recall a trial which has significant superiority for Seroquel compared to another antipsychotic.
Q. Thank you.
Dr. Macfadden, are you aware of any AstraZeneca clinical trial on Seroquel with an active comparator where Seroquel was shown to be less efficacious to a degree of statistical significance?
A. I can't recall a trial with that result, if one existed.
Q. I'm going to write down

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"Can't recall" on that.
Dr. Macfadden, are you aware of any meta-analyses on Seroquel where Seroquel was compared with active comparators where Seroquel was shown to be superior to a statistical degree of significance with any other antipsychotics?
A. I don't recall a study in which Seroquel was shown to be significantly superior in a meta-analysis with other antipsychotics, if that was your question.
Q. Dr. Macfadden, are you aware of any meta-analyses on AstraZeneca clinical trials where Seroquel was compared with active competitors and Seroquel was shown to be less efficacious to a degree of statistical significance?
A. If a study like that existed, I don't recall the results.
Q. Dr. Macfadden, are you aware of any AstraZeneca clinical trial on Seroquel where it was compared with a

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placebo control group and Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance?
A. To the best of my recollection, there was a single arm on one of the early registration studies that was either comparable to -- may not have been statistically significant, but I can't provide more details than that.
Q. So, you're just aware of one study, and you're only vaguely aware of it where Seroquel was no more efficacious than a placebo? You're just aware of one?
A. In the treatment of schizophrenia?
Q. That wasn't my question.
A. To the best of my knowledge, that was the one study I have a vague recollection about in which one of the arms may not have been statistically significant compared to placebo in the treatment of schizophrenia.

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Q. You're vaguely aware of one schizophrenia study?
A. Yes.
Q. How about nonschizophrenia studies such as study 41?
Well, maybe -- 41 could have been a schizophrenia study. I don't remember. Was it? Was the study on sustained release? I can't remember what the patient population was. I can find out.
Let me just ask, are you familiar with study 41?
A. I don't have a recollection of what study that number pertains to or the results.
Q. Given your answer about whether there's any clinical trial on Seroquel compared with a placebo controlled group where Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance, when you gave your answer, you were not aware of study 41?

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A. I don't recall the design of study 41 or what the results were.
Q. Okay.
When giving your answer about any clinical trial on Seroquel compared with the placebo where Seroquel was shown to be no more efficacious than a placebo to a degree of statistical significance, did you know about study 100?
A. I believe I gave my answer regarding schizophrenia, and I believe study 100 had something to do with bipolar disorder.
Q. In that study, 100, Seroquel was shown to be no more efficacious than an inert placebo, true?
A. I can't recall the specifics. However, there may have been a study in which Seroquel or placebo was added on to another medication.
Q. It was an adjunct study, Doctor. It was an adjunct mania study, as was study 99. When you gave the

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answer to the question about Seroquel being no more efficacious than a placebo, were you aware of studies 104 and 105?
A. I'd like to go back to the previous question. If it is an add-on study, it's not really a comparison of the second drug versus placebo since medications are already being taken.
Q. We'll debate that with somebody else, but let's make sure we're really clear because I do know about study 100. And what you did is you at AstraZeneca in the clinical trial gave some patients a combination of placebo and lithium and a medication that starts with a D, I can't pronounce it, divalproex. How do you pronounce that medication? You know what I'm talking about?
A. I think that's divalproex.
Q. Study 99, and I'm bad with divalproex, and I will probably butcher the name, I can't get it and I just studied it, and I just won't do it right.

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But study 100 combined a placebo with lithium or a placebo with divalproex versus Seroquel with lithium and Seroquel with divalproex, right?
MR. MCCONNELL: Objection to form.
THE WITNESS: That's my recollection of the general design, yes.
BY MR. ALLEN:
Q. Yes. Then when we compared the patients who were on placebo and lithium and placebo -- excuse me.
When we compared the patients who were on placebo and lithium with the patients who were on Seroquel and lithium in the primary endpoint, Seroquel was no more efficacious than the placebo arm, right?
A. No more effective than lithium alone compared -- and adjunct to placebo.
Q. Right.
Now, I'm going to go back

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to the specific marketing point you're referring to. However, when efficacy or efficaciousness is discussed, it often implies a combination of efficacy and tolerability.

MR. ALLEN: Objection, nonresponsive, completely.

BY MR. ALLEN:

Q. Doctor, did your company ever go out and tell anybody anywhere at any time that Seroquel is more efficacious than another second generation antipsychotic?

A. I don't know.

Q. Based upon the clinical trial data that you are aware of, could AstraZeneca honestly and truthfully go out and tell anybody Seroquel is more efficacious than another second generation antipsychotic?

MR. MCCONNELL: Objection to form.

THE WITNESS: To the best of

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my knowledge, there were no studies which showed a statistically significant advantage for Seroquel over competitors.

BY MR. ALLEN:

Q. Therefore, if any AstraZeneca employee or representative ever told anybody that our product, Seroquel, is superior on efficacy to another second generation antipsychotic, that would be a lie, wouldn't it?

MR. MCCONNELL: Objection to form.

THE WITNESS: With my understanding of the studies, they would be incorrect with that, yes.

BY MR. ALLEN:

Q. That's a nice way of saying it. It would be incorrect for anybody from AstraZeneca to ever have represented that Seroquel is more efficacious than any other second generation antipsychotic, right?

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MR. MCCONNELL: Objection to form.

BY MR. ALLEN:

Q. It would be incorrect?

A. As I say, I was not and I am not aware of any studies such as that that would show superior efficacy. Based on my recollection of the studies there, that would be incorrect, yes.

Q. That's a nice way of putting it. Another way of putting it, it would be false and untrue for AstraZeneca to have represented based upon the AstraZeneca clinical trial data that Seroquel was superior in efficacy to any other second generation antipsychotic, true?

MR. MCCONNELL: Objection to form.

THE WITNESS: Based on what I recall from the clinical trials, it would be incorrect to assert that Seroquel was more efficacious based on a lack of statistical

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superiority as I can recall it.

BY MR. ALLEN:

Q. It would not only be incorrect, it would be false, it would be untrue, and to put it bluntly, it would be a lie, true?

MR. MCCONNELL: Objection, form.

THE WITNESS: It would be incorrect. I can't speak about your other characterizations.

BY MR. ALLEN:

Q. Not only would it be untrue to say that Seroquel was more efficacious than a second generation antipsychotic, it would be untrue to say that Seroquel was more efficacious than a first generation antipsychotic, true?

A. It depends how the word "efficacious" is used. If it pertains to combinations of efficacy and safety, it is different than just efficacy alone.

Q. I'm talking about efficacy alone, Doctor. It would be untrue and

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wrong for AstraZeneca to represent that Seroquel was more efficacious than any first generation antipsychotic, true?

MR. MCCONNELL: Objection to form. Objection to the extent it calls for a legal conclusion.

THE WITNESS: To the best of my recollection, as I stated, there was no clinical trial in which Seroquel demonstrated statistically significant superiority over a typical antipsychotic, thus, to the best of my recollection, that would be false.

BY MR. ALLEN:

Q. Thank you.

And when you said "a typical," in that sentence, you were using "a" and "typical" as two separate words, right?

A. Yes.

Q. Now, when making a risk/benefit analysis, one must look at

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both efficacy and safety, true?

A. If a clinician is deciding on a medication, presumably they look at both safety and efficacy, yes.

MR. ALLEN: What's my next Exhibit Number? 39?

THE COURT REPORTER: Yes.

- - -

(Whereupon, Deposition Exhibit Macfadden 39, Handwritten document (1 page), was marked for identification.)

- - -

BY MR. ALLEN:

Q. Doctor, you have to look at the screen for 39 because you and I are going to create this together. You have the screen, you can see the exhibit?

A. Yes.

Q. The SQ on the left-hand column, we're going to have that stand for Seroquel. That's a common abbreviation in your company for Seroquel, is it not?

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A. I think SQL was more common, but, yes.

Q. You know what, SQL, that's Seroquel, right?

A. Yes.

Q. All others, we're going to put "all other antipsychotics." I'm a real bad speller, by the way.

Now, you've told us in regard to efficacy, which I'm going to put over here in the left hand -- you've given us your answer in regard to efficacy, and there was no superiority for Seroquel in the data that you're aware of, true?

A. There was no statistically significant superiority regarding efficacy endpoints to the best of my knowledge that I can recall.

Q. And so I would like to add "statistical." By the way, in the scientific field there at AstraZeneca, that's what's important, isn't it, statistical significance?

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A. Statistical significance and clinical significance are both important.

Q. You're a pharmaceutical physician. That's how you described yourself yesterday. Do you remember that?

A. I described myself as a physician being employed by a pharmaceutical company, therefore, a pharmaceutical physician, yes.

Q. I didn't use the term. Do you recall in an answer to my question, you volunteered that you said I am a pharmaceutical physician? Do you recall that?

MR. MCCONNELL: Objection to form.

THE WITNESS: Yes.

BY MR. ALLEN:

Q. In fact, I remember I asked you something, and you said, well, Mr. Allen, that was before I became a pharmaceutical physician. And I asked you when you became a pharmaceutical

shall appear in the ''Description'' section of the labeling, whether or not it also appears in a ''Product Title.''

(e) The labeling shall contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

[44 FR 37462, June 26, 1979]

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) *Description.* (1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) *Clinical Pharmacology.* (1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement ''The following in vitro data are available but their clinical significance is unknown.''

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) *Indications and Usage.* (1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g.,

chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjuction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the ''Dosage and Administration'' section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) *Contraindications.* Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state ''None known.''

(e) *Warnings.* Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the ''Indications and Usage'' section of the

labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectivenes for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the ''Adverse Reactions'' section of the labeling.

(f) *Precautions.* Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) *General.* This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) *Information for patients.* This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the ''Precautions'' section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

(3) *Laboratory tests.* This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) *Drug interactions.* This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the ''Dosage and Administration'' section of the labeling rather than under this subsection of the labeling.

(ii) *Drug/laboratory test interactions.* This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) *Carcinogenesis, mutagenesis, impairment of fertility.* This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the

significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the ''Warnings'' section of the labeling. Also, under ''Precautions,'' the labeling shall state: ''See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility.''

(6) *Pregnancy.* This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(*a*) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ''Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: ''Reproduction studies have been performed in (*kinds of animal*(*s*)) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*).'' The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*b*) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: ''Pregnancy Category B. Reproduction studies have been performed in (*kind*(*s*) *of animal*(*s*)) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.'' If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: ''Pregnancy Category B. Reproduction studies in (*kind*(*s*) *of animal*(*s*)) have shown (*describe findings*) at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.'' The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*c*) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: ''Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to

have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.'' The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: ''Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed.'' The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(*d*) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: ''Pregnancy Category D. See 'Warnings' section.'' Under the ''Warnings'' section, the labeling states: ''(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.''

(*e*) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: ''Pregnancy Category X. See 'Contraindications' section.'' Under ''Contraindications,'' the labeling shall state: ''*(Name of drug)* may (*can*) cause fetal harm when administered to a pregnant woman. *(Describe the human data and any pertinant animal data.) (Name of drug)* is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.''

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) *Labor and delivery.* If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) *Nursing mothers.* (i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: ''Because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ''Caution should be exercised when (*name of drug*) is administered to a nursing woman.''

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (*name of drug*) (or, ''Because of the potential for tumorigenicity shown for (*name of drug*) in (*animal or human*) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.'' If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: ''It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (*name of drug*) is administered to a nursing woman.''

(9) *Pediatric use.* (i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the ''Indications and Usage'' section of the labeling, and appropriate pediatric dosage information shall be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or ''Clinical Studies'' section. As appropriate, this information shall also be contained in the ''Contraindications,'' ''Warnings,'' and elsewhere in the ''Precautions'' sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the ''Pediatric use'' subsection of the labeling and discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' and ''Clinical Studies'' sections. Appropriate pediatric dosage shall be given under the ''Dosage and Administration'' section of the labeling. The ''Pediatric use'' subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the

''Contraindications,'' ''Warnings,'' and elsewhere in the ''Precautions'' sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the ''Pediatric use'' subsection of the labeling shall contain either the following statement, or a reasonable alternative: ''The safety and effectiveness of (*drug name*) have been established in the age groups __ to __ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).'' Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the ''Clinical Pharmacology'' or the ''Clinical Studies'' section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the ''Clinical Pharmacology'' section. Pediatric dosing instructions shall be included in the ''Dosage and Administration'' section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the ''Pediatric use'' subsection and, as appropriate, in the ''Contraindications,'' ''Warnings,'' ''Precautions,'' and ''Dosage and Administration'' sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the ''Pediatric use'' subsection of the labeling shall contain an appropriate statement such as ''Safety and effectiveness in pediatric patients below the age of (__) have not been established.'' If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications'' or ''Warnings'' section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: ''Safety and effectiveness in pediatric patients have not been established.'' If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications'' or ''Warnings'' section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA

may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the ''Contraindications,'' ''Warnings,'' or ''Precautions'' section.

(10) *Geriatric use.* (i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the ''Indications and Usage'' section of the labeling, and appropriate geriatric dosage shall be stated under the ''Dosage and Administration'' section of the labeling. The ''Geriatric use'' subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the ''Geriatric use'' subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under ''Clinical Pharmacology'' or the ''Clinical Studies'' section. As appropriate, this information shall also be contained in ''Contraindications,'' ''Warnings,'' and elsewhere in ''Precautions.''

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the ''Geriatric use'' subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The ''Geriatric use'' subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection shall include the following statement:

''Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.''

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the ''Geriatric use'' subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), __ percent were 65 and over, while __ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified

differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the ''Geriatric use'' subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the ''Contraindications,'' ''Warnings,'' ''Dosage and Administration,'' or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the ''Geriatric use'' subsection of the labeling and in detail under the ''Clinical Pharmacology'' section. The ''Clinical Pharmacology'' section and ''Drug interactions'' subsection of the ''Precautions'' section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the ''Geriatric use'' subsection shall include the statement:

''This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.''

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the ''Geriatric use'' subsection of the labeling, or, if appropriate, the hazard shall be stated in the ''Contraindications,'' ''Warnings,'' or ''Precautions'' section of the labeling, and the ''Geriatric use'' subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

''Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely.''

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) *Adverse Reactions.* An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall

be expressed in rough estimates or orders of magnitude essentially as follows: ''The most frequent adverse reaction(s) to (*name of drug*) is (are) (*list reactions*). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (*list reactions*), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (*list reactions*).'' Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The ''Warnings'' section of the labeling or, if appropriate, the ''Contraindications'' section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) *Drug Abuse and Dependence.* Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) *Controlled Substance.* If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) *Abuse.* This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) *Dependence.* This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) *Overdosage.* Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the ''Clinical Pharmacology'' section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) *Dosage and Administration.* This section of the labeling shall state the

recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: ''Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.''

(k) *How Supplied.* This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) *Animal Pharmacology and/or Animal Toxicology.* In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) *''Clinical Studies'' and ''References''.* These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the ''Clinical Studies'' or ''References'' section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks

shall also be identified or discussed in the appropriate section of the labeling for the drug.

[44 FR 37462, June 26, 1979, as amended at 55 FR 11576, Mar. 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998]

§ 201.58 Requests for waiver of requirement for adequate and well-controlled studies to substantiate certain labeling statements.

A request under § 201.57(b)(2)(ii), (c)(2), (c)(3)(i), (c)(3)(v), (f)(9), and (g)(4) for a waiver of the requirements of § 314.126(b) of this chapter shall be submitted in writing as provided in § 314.126(b) to the Director, Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or, if applicable, the Director, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. The waiver shall be granted or denied in writing by such Director or the Director's designee.

[55 FR 11576, Mar. 29, 1990, as amended at 70 FR 14980, Mar. 24, 2005]

§ 201.59 Effective date of §§ 201.56, 201.57, 201.100(d)(3), and 201.100(e).

(a) On and after December 26, 1979, no person may initially introduce or initially deliver for introduction into interstate commerce any drug to which §§ 201.56, 201.57, 201.100(d)(3) apply unless the drug's labeling complies with the requirements set forth in the regulations, with the following exceptions:

(1) If the drug is a prescription drug that is not a biologic and not subject to section 505 of the act (21 U.S.C. 355), and was not subject to former section 507 of the act (21 U.S.C. 357, repealed 1997), §§ 201.56, 201.57, and 201.100(d)(3) are effective on April 10, 1981.

(2) If the drug is a prescription drug that on December 26, 1979 is (i) a licensed biologic, (ii) a new drug subject to an approved new drug application or abbreviated new drug application under section 505 of the act or (iii) an antibiotic drug subject to an approved antibiotic form, §§ 201.56, 201.57, and 201.100(d)(3) are effective on the date listed below for the class of drugs to which the drug belongs. Dates are also listed below for the submission of supplemental applications, amendments, and license changes.

(3) If the drug is approved after December 26, 1979 but is a duplicate of a drug approved on or before that date (for example, a drug approved under an abbreviated new drug application or an antibiotic form), §§ 201.56, 201.57, and 201.100(d)(3) are effective on the date listed below for the class of drugs to which the drug belongs. Dates are also listed below for the submission of supplemental applications, amendments, and license changes.

Effective	Revised labeling due	Drug class	Mail routing code
		BIOLOGICS	
Nov. 1, 1982	Nov. 1, 1980	Bacterial vaccines and antigens with no U.S. standard of potency.	HFB–240
Do	do	Skin test antigens	HFB–240
Nov. 1, 1982 [1]	Nov. 1,1980 [2]	Bacteral vaccines and toxoids with standards of potency.	HFB–240
Do	do	Viral and rickettsial vaccines	HFB–240
Do	do	Allergenic extracts	HFB–240
Do	do	Blood and blood derivatives	HFB–240
		NEW DRUGS AND ANTIBIOTIC DRUGS	
Nov. 1, 1982	Nov. 1, 1980	Antiarrhythmics	HFD–110
Do	do	Replenishers and regulators of electrolytes and water balance	HFD–110, HFD–510, and HFD–160
Do	do	Anticonvulsants	HFD–120
Do	do	Adrenal corticosteroids	HFD–510 and HFD–150
Do	do	Aminoglycosides	HFD–520
Do	do	Scabicides	Do.
Do	do	Pediculicides	Do.
Do	do	General anesthetics	HFD–160
Dec. 1, 1982	Dec. 1, 1980	Antivirals	HFD–520
Do	do	Dermatologics	Do.
Jan. 1, 1983	Jan. 1, 1981	Glaucoma ophthalmics	HFD–520
Do	do	Topical otics	Do.

Id : i.m.c22c37e56740fa1f408e63eba6fa447b
CN : S339-E01167234
Date : Tuesday, December 4, 2007 1:39:49 PM GMT
From : "Rak, Ihor W" <ihor.rak@astrazeneca.com>
To : "Goldstein, Jeffrey M" <jeffrey.goldstein@astrazeneca.com>
Subject : Re: information
Custodians : Goldstein, Jeffrey

From: Rak, Ihor W

Sent: Tuesday, December 04, 2007 1:40 PM

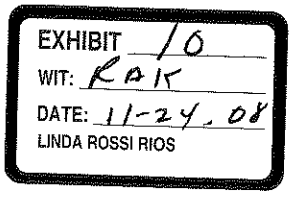
To: Goldstein, Jeffrey M

Subject: Re: information

Jeff

Thanks for reaching out to me - I will look into this and we should discuss. When is your must decide date so I know how much time I have?

Ihor



Sent from my BlackBerry Wireless Handheld

----- Original Message -----

From: Goldstein, Jeffrey M

To: Rak, Ihor W

Sent: Mon Dec 03 19:49:04 2007

Subject: information

Dear Ihor,

I need to make a very difficult decision over the next few weeks and I wanted to reach out to you for advice. A few weeks ago we chatted briefly and I told you that I was anticipating a promotion to Senior Director but things have not progressed as fast as I had hoped, and the recent reorganization may have removed this from peoples radar screens. I was counting on this promotion to bring me to Band 7 and allow the cap on my salary to be removed because over the past three years I have not received a raise. This was because my salary in relation to the MRP for Band 6 is above the accepted limits. Although I have received a lump sum each year in lieu of a raise, it has not figured into my bonus or pension. You can imagine how frustrated I am in view of my excellent performance reviews. I recently did some calculations and if I were to retire at the end of this year the company would have to add 6 weeks of banked vacation plus an additional week that I was allowed to carryover into 2008. That would make 2007 my best grossing year (assuming my bonus is on par with previous years) and my pension would increase. That is a very attractive option for me. However, I am hesitant to act on this urge as I feel I still have a lot to offer this company and my passion for Seroquel has far from ended. And, there is a lot going on with Seroquel under the pretense of science that needs serious review. So to be very frank with you and the reason for this email is to ask the following questions - am I being considered for promotion to Senior Director, when will this likely happen, and will my salary increase appropriately? Sorry if I am putting you in a difficult situation but I need to make a decision very soon and you are the only one who can provide me with the answers to those questions.

I will be traveling this week to Budapest to make 2 Seroquel presentations at IFMAD, and then on vacation for the rest of the year although I am giving up several vacation days to handle urgent matters not the least of which is to continue to meet with the attorneys who are preparing me for my January deposition. I regularly check my email when home (a habit I cannot seem to break) so except for my time in Budapest I will look for a response from you. I would also welcome some time with you to discuss this further if you think that would be best and would happily give up some vacation time to meet at your convenience.

I truly hope that AZ will reward and recognize me with a promotion but more importantly give me the opportunity to take on a more senior leadership role. I truly believe our group needs a senior person to step in and question the science being presented at several levels. I look forward to hearing back from you.

Sincerely,

Jeff

Clinical Study

The weight profile of SEROQUEL over the long term

Authors: Brecher M, Rak IW, Melvin K, et al.

Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

Journal: *International Journal of Psychiatry in Clinical Practice* 2000;4:287-291.

Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - —178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - —Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - —BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

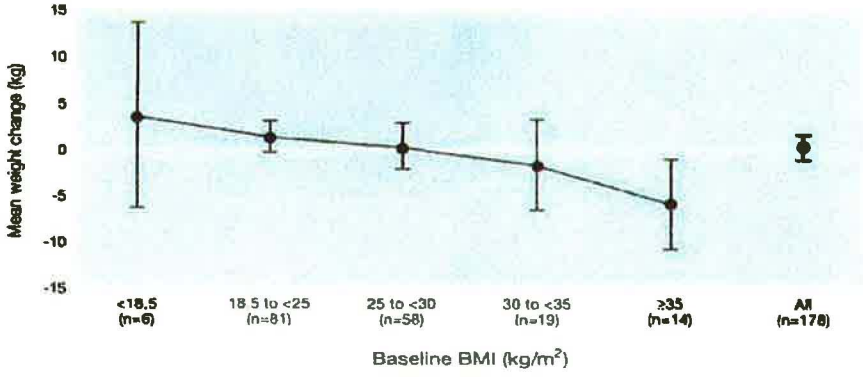
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*Last recorded weight measurement

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



 International Journal of Psychiatry in Clinical Practice 2000 Volume 4 Pages 287–291

The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

M BRECHER,[1] IW RAK,[1] K MELVIN[2] AND AM JONES[2]

AstraZeneca, [1]Wilmington, DE, USA and [2]Alderley Park, Macclesfield, Cheshire, UK

Correspondence Address
Dr Martin Brecher, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE, USA
Tel: +1 (302) 886 2634
Email: martin.brecher@astrazeneca.com

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INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 *kg/m*^{2}*) and severely obese patients (BMI* ≥ 35 *kg/m*^{2}*).*

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[1] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
<50 kg	5
50–70 kg	171
71–90 kg	164
>90 kg	59

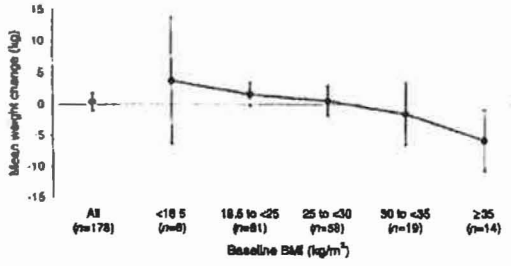


Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg

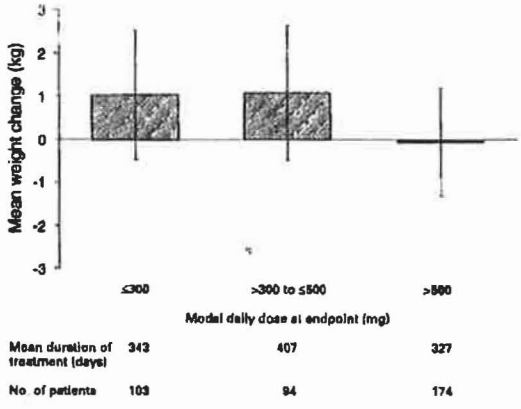


Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m^2)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5<25	81	468	539	1.6
≥25<30	58	466	607	0.53
≥30<35	19	514	551	−1.53
≥35	14	483	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,16,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m^2), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.

Unknown

From: Aked Dominic DM
Sent: Thursday, October 26, 2000 9:30 PM
To: Rak Ihor IW
Cc: O'Brien Shawn SP; Shadwell Pamela PG; Holdsworth Debbie D; Jones Martin AM - PHMS
Subject: RE: Data for weight neutral slide

Hi Ihor

Many thanks for this important feedback.

I agree we need to be able to tell a convincing story to our internal and external customers. I'm sure we can do this.

- Re US PI: From what I can see any mention of weight gain in the US PI relates to short-term studies. We may be able to make a clear distinction between this clinical situation and long-term treatment (that is, acutely psychotic relapse versus long-term maintenance). Presumably the latter is what is important clinically given that patients receive long-term treatment.

A promotional claim ***'Seroquel is weight neutral during long-term treatment*** should help to make this distinction.

- There may be a rationale to explain why acutely psychotic patients may gain weight in the short term, following effective therapy. The relief of negative symptoms, apathy etc, disorganised thinking, may result in return to normal activities like having regular meals.

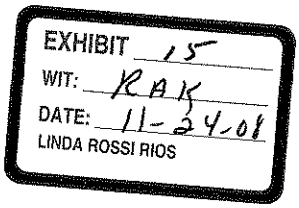
There are useful indicators in the patient satisfaction study to support the view that effective long term therapy with Seroquel helps to normalise eating.

Benefits noticed in last 6 mo by patients on Seroquel
55% patients prepare and cook meals
64% go shopping for food/personalitems
73% eat more normally
Page 25 Figure 4C Clear Perspectives Vol 2 issue 3

One additional comment (where there's a ying there's a yang): if we look at incidence of patients gaining >7% baseline weight, we should also consider looking at patients losing >7% baseline weight, or what would be considered a clinically significant weight loss.

Kind regards

Dom

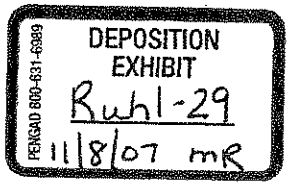


From: Rak Ihor IW
Sent: 25 October 2000 02:16
To: 'Rob Kite'; Holdsworth Debbie D; Jones Martin AM - PHMS
Cc: Shadwell Pamela PG; Ashworth Phillip P; Aked Dominic DM; Gavin Jim JP; O'Brien Shawn SP
Subject: RE: Data for weight neutral slide

All

I had the pleasure of presenting 5 weight slides (from the International Speaker's Training meeting) to the US SEROQUEL Product Team.

The titles of the 5 slides were; SEROQUEL-minimal effect on weight long term; SEROQUEL- neutral effect on weight at all doses; 3 slides-- Long-term SEROQUEL monotherapy has neutral effect on weight (1 with confidence intervals, another n=112 of 53 weeks exposure and longer shifts in BMI category, and another shifts in BMI category in obese/severely obese patients).



53

They had some very good suggestions based on their having to deal with the US label which states that SEROQUEL causes dose related weight gain (NDA dataset).

1. Best to tell a story. Data from clinical trials showed this, but limitations are these. hence another dataset analysed

2. using different datasets raises suspicions if not adequately explained and justified.

3. when selecting a cohort of patients who were treated for 26 or 53 weeks minimum, suspicions are immediately raised about the patients "censored": what was their mean weight change. For both cohorts of patients (those displayed and those censored) how many experienced adverse events (weight gain >7% of body weight), how any discontinued from the OLE due to weight gain, etc

4. BMI shifts not quickly understood; patients can not shift fromtheseverely obese BMI category (already mentioned)

Certainly, the more of these comments that we examine and address, the more confidence we will have in our weight neutral message.

Ihor

From: Jones Martin AM - PHMS
Sent: Friday, October 20, 2000 10:25 AM
To: 'Rob Kite'; Holdsworth Debbie D
Cc: Shadwell Pamela PG; Ashworth Phillip P; Rak Ihor IW; Aked Dominic DM; Gavin Jim JP
Subject: RE: Data for weight neutral slide
Importance: High

Rob

Please find attached a word document containing the data that you need. There are 40 pages in totally. The first 20 refer to all doses, the last 20 to data from within the 150-750 mg dose range.

In yesterday's Communication Planning Team meeting, it was decided to focus on the all dose cohort, for which we have 178 schizophrenic patients, with weight data beyond day 182, with BMI data. This data is slightly different to that previously included in my slide.

The summary data for this cohort starts on page 6, with :

	N	Mean	LCL	UCL	Median	Min	Max	Std Err	t Prob>|t|	TINV
All	178	0.412	-0.910	1.743	-0.450	-27.00	27.000	0.991	0.674	0.612	0.728	1.973

From this you should be able to get all the required data. The following page contains mean dose data for the entire cohort.

The next dozen or so pages divide these 178 patients into demographic sub-groups i.e. baseline BMI, gender, age group, race, mean dose group (interesting ?). All the tables should contain data for 178 patients !

The analyses are then repeated for the 150-750 mg group.

Hope this helps.

I am away on holiday next week, but Pamela, or Phill Ashworth may be able to help you with any queries.

Regards

AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

Date July 2008

SEROQUEL™ (quetiapine fumarate)
Clinical Overview on Weight Gain in pediatric patients

Authors:

Leigh Jefferies M.D.
Global Safety Physician
Patient Safety, Wilmington, DE

Eva S.K. Alam, M.S., Pharm.D., RPh
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

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LIST OF TABLES

1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL is to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

1.2 Proposed label change

The following text will be added to Section 4.8 *Undesirable effects* of the SEROQUEL CDS under a subheading of *Children and adolescents.*

Children and adolescents

The same ADRs described above for adults apply to children and adolescents. The following table summarizes ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained $\geq$ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained $\geq$ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Since clinical trials in pediatric patients have been conducted with SEROQUEL and not SEROQUEL XR this change applies only to the SEROQUEL CDS.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

5.1.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer-term open-label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a brief description of these three trials.

- D1441C00112: a 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D1441C00149: a 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D1441C00150: a 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.2 Acute placebo-controlled data

5.1.2.1 D144C00112

Mean increase in body weight

In study D144C00112, mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine-treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (23.21% in the 400 mg/day and 18.18% in the 800 mg/day) had ≥7% weight gain at Day 42 compared to the placebo-treated patients (6.82%) (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.2)	10 (18.2)	3 (6.8)

5.1.2.2 D144C00149

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine-treated group, 1.7 kg in the 600 mg quetiapine-treated group and 0.4 kg in the placebo group. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (see Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (14.47% in the 400 mg/day and 9.88% in the 600 mg/day) had ≥7% weight gain at Day 21 compared to placebo-treated patients (0%) (see Table 4).

Table 4 D144C00149: Patients with ≥7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.5)	8 (9.9)	0 (0)

5.1.3 Longer-term open-label pediatric data

5.1.3.1 D1441C00150

Study D1441C00150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study D144C00112) and in children and adolescents with bipolar I disorder (continuing from Study D144C00149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania. Sixty-three percent of patients (241) completed 26 weeks of therapy with quetiapine.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 5.

Table 5 **Study D1441C00150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.3	113	64.8	19.2	175	65.7	18.2
Change from 112 DB BSLN	62	4.1	8.5	113	4.8	10.8	175	4.6	10.0
Change from 150 OL Baseline	62	4.3	6.9	113	2.8	10.1	175	3.3	9.1
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.9	136	64.5	18.4	200	65.8	19.6
Change from 149 DB BSLN	64	5.8	6.4	136	5.1	5.7	200	5.3	5.9
Change from 150 OL Baseline	64	5.5	5.8	135	3.2	4.8	199	4.0	5.2
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.3	249	64.7	18.7	375	65.7	19.0
Change from DB BSLN	126	5.0	7.50	249	5.0	8.3	375	5.0	8.1
Change from 150 OL Baseline	126	4.9	6.4	248	3.0	7.6	374	3.7	7.3

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial D1441C00150, the mean change in weight from OL baseline was 4.4 kg.

Patients with ≥7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 6).

Table 6 **Study D1441C00150: Patients with ≥ 7% weight gain (Summary safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥7% increase in weight from OL baseline.

5.1.4 Additional analysis of Pediatric data

5.1.4.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI), since with BMI, the weight is adjusted for height (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z-score taking into consideration the age and gender of the subject. Z-scores are able to show how different a child's weight or BMI is from the average children of the same height (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z-score of 0.5 over any duration of time (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study D1441C00150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group (see Table 7).

Table 7 **Study D1441C00150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.2	113	**-0.1**	1.4	175	**0.0**	1.3
Week 26	41	0.4	1.1	86	0.1	1.22	127	0.2	1.2
Final Visit	62	**0.5**	1.0	113	**0.2**	1.3	175	**0.3**	1.2
149 DB Baseline	67	**1.0**[a]	1.0	138	**0.9**[a]	1.1	205	**0.9**[a]	1.0
Week 26	37	1.2	1.0	77	1.2	1.0	114	1.2	1.0
Final Visit	63	**1.2**	1.0	135	**1.0**	1.0	198	**1.1**	1.0
DB Total Baseline	129	**0.6**	1.2	251	**0.4**	1.3	380	**0.5**	1.3
Week 26	78	0.8	1.1	163	0.6	1.2	241	0.7	1.2
Final Visit	125	**0.9**	1.0	248	**0.7**	1.2	373	**0.7**	1.2

[a] The mean BMI Z score at baseline is much higher for the 149 population

Table 8 below shows patients who had a ≥ 0.5 shift in BMI Z-score during trial D1441C00150 from both DB baseline and OL baseline and by indication. Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Table 8 **Patients with ≥ 0.5 shift in BMI Z score in Study D1441C00150 by indication**

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Patients with ≥0.5 shift in standardized BMI Z-score in Study D1441C00150 by age group

A similar percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (28% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (25% at EOT) from the DB baseline (see Table 9).

A higher percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (24% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (8.6% at EOT) from the OL baseline (see Table 9).

A similar percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (22% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (20.1% at EOT) from the DB baseline (see Table 9).

A higher percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (21% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (11.7% at EOT) from the OL baseline (see Table 9).

Table 9 **Patients with ≥0.5 shift in BMI Z score in Study D1441C00150 by age group***

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.1.4.2 Overall summary of pediatric clinical trial data

In trial D1441C00112, the mean increase in body weight was 2 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty-one percent of quetiapine patients and 7% of placebo patients had gained ≥7% of their body weight.

In trial D144C00149, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine patients and 0% of placebo patients had gained ≥7% of their body weight.

In trial D1441C00150, where 63% of patients (241/380) completed 26 weeks of therapy with quetiapine, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients had ≥7% increase in body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL Core Data Sheet and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL:

Name of the expert: Leigh Jefferies, MD
Global Safety Physician
Patient Safety

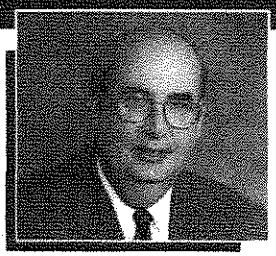
Signature:

Address:
1800 Concord Pike
Wilmington, DE 19850

Date:

According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.

Managing Weight Gain and Diabetes in Schizophrenia



A Patient Case Study

From the files of
Michael J. Reinstein, MD

Forest Foundation, Inc.
Clinical Research Department
Community Mental Health
Chicago, Illinois

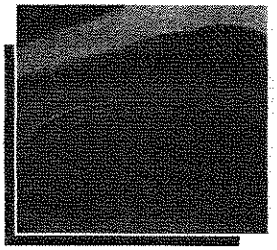


EXHIBIT 31
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

Patient Presentation

- A 49-year-old white male, unemployed, with a long history of psychiatric hospitalizations dating from age 25
- His various diagnoses include acute schizophrenic episode, paranoid schizophrenia, bipolar disorder, and schizoaffective disorder
- The patient also has a history of alcohol abuse

Past Medical/ Psychiatric History

- The patient was first hospitalized in 1976 with religious delusions, auditory hallucinations, and withdrawal
- He was subsequently hospitalized on several different occasions and followed on an outpatient basis after each discharge

Personal History

- There is no family history of psychiatric illness
- The patient was married with a son but has not had contact with either his wife or son for over 20 years
- He has not been gainfully employed for over 15 years
- He lives sporadically with either his mother or in homeless shelters

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. If its signs and symptoms appear, discontinuation should be considered.

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

Please see accompanying full prescribing information.

Mental/Physical Evaluation

- At presentation, the patient was alert and oriented to time, place, and person, maintained good eye contact, and was stable and in a cooperative mood
- Intelligence appeared to be within normal range
- He denied any hallucinations or ideas of reference
- No EPS, rigidity, or ataxia; no suicidal or homicidal ideations were expressed
- Judgment and reality contact were impaired, he appeared to have no insight, and he frequently laughed inappropriately in response to internal stimuli
- The patient answered questions only after considerable pauses—very briefly and in a low tone and volunteered no information whatsoever
- Physical evaluation revealed a patient overweight by approximately 10 lb

Treatment with SEROQUEL, like other antipsychotics, may result in somnolence, especially during initial dose titration.

Rationale for SEROQUEL Therapy

- Previous treatment with olanzapine 10 mg/day resulted in significant weight gain (10 lb) and subsequent development of type II diabetes (NIDDM)
- Accu-Chek™ was scheduled tid with sliding scale of Humulin® insulin

"This patient demonstrated some classic negative symptoms—blunted affect, emotional withdrawal, poor rapport, lack of spontaneity. Negative symptoms can often be very difficult to treat. We chose SEROQUEL for this patient because in our experience it provides excellent results with negative psychotic symptoms, and weight gain with SEROQUEL hasn't been an issue."

—Michael J. Reinstein, MD

SEROQUEL Dosing Regimen

- Olanzapine therapy was discontinued due to weight gain and the development of diabetes
- SEROQUEL was initiated at 150 mg/day for 1 week
- The SEROQUEL dose was then increased to 300 mg/day where it remains

Response to SEROQUEL

- The patient has shown a positive response to SEROQUEL, becoming more spontaneous, more interested in his surroundings, and has demonstrated improved interactions with others
- Blood glucose levels were brought under control, permitting the substitution of an oral hypoglycemic agent for insulin treatments
- Metabolic stability was maintained, allowing the patient to discontinue the hypoglycemic agent and return to a normal diet
- Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on olanzapine

"Our laboratory data revealed a normalization of serum glucose levels which is valid proof of improvement of diabetes and metabolic stabilization. His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also relieved that he no longer has to take daily insulin injections."

—Michael J. Reinstein, MD

Follow Up

- After 7 months, the patient remains well on SEROQUEL 300 mg/day
- The patient is currently taking part in a research study, where he perceives himself as a partner in a joint endeavor. He has achieved clinical improvement and a better quality of life
- He denies having any side effects and is considered competent to handle his own funds and supervised self-medication

"We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications."

—Michael J. Reinstein, MD

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported, and prescribing should be consistent with the need to minimize the risk.

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets
For a more normal life

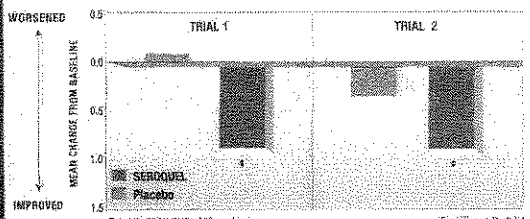
Please see accompanying full prescribing information.

The Strength to Control Both Positive and Negative Symptoms

Across well-controlled trials

Consistent Efficacy in the Treatment of Positive Symptoms[1,2]...

Mean Change in BPRS* Positive Symptom Cluster Scores (LOCF)[1,4†]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)

*Significant $P<0.01$

- **SEROQUEL significantly reduced positive symptom scores**

SEROQUEL was compared with placebo in the following well-controlled, 6-week, acute-phase, multicenter trials.

Trial 1: fixed doses of 75, 150, 300, 600, and 750 mg/day of SEROQUEL (n=255), placebo (n=51).

Trial 2: titrated doses up to 250 mg/day (low dose, n=94) and up to 750 mg/day (high dose, n=96) of SEROQUEL, placebo (n=96).

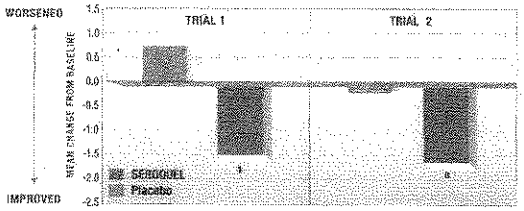
*BPRS: Brief Psychiatric Rating Scale is a clinical assessment tool that measures a combination of 18 individual positive, negative, and general symptom items. The BPRS positive symptom cluster score is the mean of 4 of the 18 individual symptom items for the clinical assessment of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

†LOCF: Last Observation Carried Forward.

Precautions listed in the label include orthostatic hypotension and the risk of cataract development.

...and Consistent Efficacy in the Treatment of Negative Symptoms[1,2]

Mean Change in SANS[5] Summary Scores (LOCF)[1,4]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)

*Significant $P<0.01$
†Significant $P=0.02$

- **SEROQUEL significantly reduced negative symptom scores**

[5]SANS: Modified Scale for the Assessment of Negative Symptoms is used to assess the negative symptoms associated with schizophrenia. The SANS summary score is a total of 5 global items: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention.

The most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).

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quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

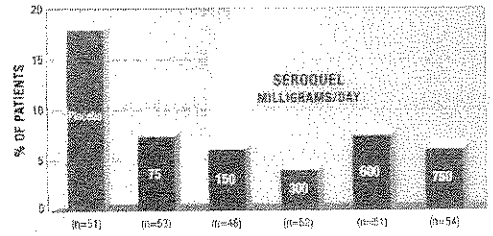
For a more normal life

Please see accompanying full prescribing information.

Outstanding Overall Tolerability Across the Entire Dose Range

Across the entire dose range,* an EPS† profile no different from placebo

EPS Adverse Events by Dose[‡]

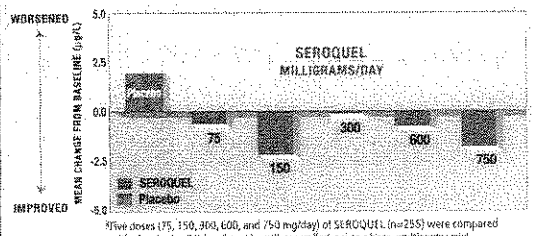


*In a 6-week, acute-phase, placebo-controlled trial.
†EPS: Extrapyramidal Symptoms were defined as dystonia, akathisia, and parkinsonism.
‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- No dose-related EPS were associated with treatment with SEROQUEL® (quetiapine fumarate)[5]

Across the entire dose range, plasma prolactin levels no different from placebo[5]

Mean Change in Plasma Prolactin Levels[‡]



‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- There were no statistically significant differences in plasma prolactin levels between any group taking SEROQUEL and the placebo group[1]

Minimal Weight Gain

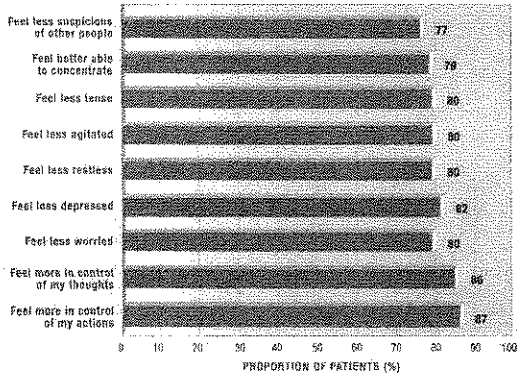
- In a recent open-label study, only 2.5% of patients treated with SEROQUEL (n=553) reported weight gain[6]

Patient Preferred

In a survey of patients (n=129) using SEROQUEL[7]

- 97% reported that they preferred SEROQUEL to previous medications
  - —Two reasons for preferring SEROQUEL were efficacy (29%) and tolerability (41%)[7]
- Benefits noticed in the last 6 months by patients using SEROQUEL

Efficacy-Related Benefits[7]



As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in all placebo-controlled clinical trials, weight gain was approximately 5 lb, which occurred mainly during the early weeks of treatment.[5]

Please see accompanying full prescribing information.

From: Hough Nick NW
Sent: 2/24/1999 8:30:56 AM
To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC; Tumas John JA
CC: Tugend Georgia GL
BCC:
Subject: RE: ECNP Abstract 'Weight gain & diabetes management'

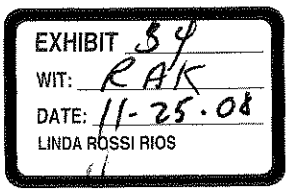
Hi John,

in principle it's the quality of the data, not the source that matters for promo claims etc. - providing, of course, that whatever the message is, that it is consistent with the totality of the data. We must not get too carried away with 'weight loss' when we know the rest of our data appears to point in the other direction, although a specific message related to the special nature of this particular finding might be possible. I need to see a full account of the data in order to be more certain at this stage. In some countries, however, a promotional claim can only be made if the data has been 'published' - usually this means a peer-reviewed journal. In the UK we can use 'data on file', but we must be prepared to supply it to anyone asking for substantiation, and if they don't like it they can complain to the relevant bodies. I guess there are different rules in the US? - as I understand it you can only make promotional claims based on the data/information in your actual labelling; I'd be interested to know more about this.

I hope this helps,

Nick

>----------
>From: Tumas John JA
>Sent: 24 February 1999 13:13
>To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K; Davies Diane DE - MMCC
>Cc: Tugend Georgia GL
>Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
>Actually, this abstract was submitted to APA, which will be the first time it is presented anywhere - that will be May 15 -20. I'm afraid that because it wasn't clear until the last minute if Dr. Reinstein was going to submit this, it never got on our abstract list.
>
>Bye the way, is it possible to make a claim from data that are not the result of a Zeneca trial?
>
> ----------
> From: Davies Diane DE - MMCC
> Sent: Wednesday, February 24, 1999 3:39 AM



> To: Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J; Bill Kevin K
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear Kevin
> If accepted, the abstract will be published at ECNP, which is September 21st 1999.
> To my knowledge this will be the first report of weight loss with seroquel - in this setting.
> kind regards
> Diane
> ----------
> From: Bill Kevin K
> Sent: 23 February 1999 22:52
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF; Owens Judith J
> Cc: Tumas John JA; Tugend Georgia GL
> Subject: RE: ECNP Abstract 'Weight gain & diabetes management'
>
> Is this the first mention of weight loss for SEROQUEL ?>
> If so when does it publish?
>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:20
> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
> Subject: ECNP Abstract 'Weight gain & diabetes management'
>
> Dear All
> Sorry for the previous e-mail which contained the abstract but no message.
> Please find attached an abstract for review. The abstract on the topic of 'management of weight gain and diabetes' is intended for submission to ECNP. The author, Dr Reinstein - a US investigator, has written this article which is reporting on his own study. This abstract has been deemed internationally important by the Communications Planning Team, therefore it is being subjected to international review. Should you have any comments on Dr Reinstein's abstract please forward them directly to John Tumas {you will see that there are some queries which need to be put to the author, these are italicised in the attachment}.
> Kind regards
> Judith Owens
> Ext: (2)8235
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
> ----------
> From: Owens Judith J
> Sent: 15 February 1999 13:04

> To: Davies Diane DE - MMCC; Rak Ihor IW; Litherland Steve S; Jones Martin AM - PHMS; Hough Nick NW; Price Anna AC; Lawrence Richard RA; Murray Michael MF
> Cc: Tumas John JA; Tugend Georgia GL; Bill Kevin K
>
> <<File: Management of Weight Gain and Diabetes by Clozapine.doc>>
>
>
>
>
>

Distinct advantages of a favorable weight profile

- Weight gain, commonly reported with some other antipsychotics, is associated with particular morbidities:
  —Type 2 diabetes, hypertension, coronary heart disease, cerebrovascular disease, certain cancers, and respiratory problems
- Minimal weight gain may reduce the likelihood that treatment with SEROQUEL will lead to diabetes and other morbidities associated with weight gain.
- Among patients taking antipsychotic medication, weight gain has been shown to cause more distress than other common adverse events

The most common adverse events associated with the use of SEROQUEL are dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The majority of adverse events are mild or moderate.[1]

In premarketing trials, the most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).[1]

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.[1]

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported.[1]

The safety and effectiveness of SEROQUEL in pediatric patients have not been established.[1]

As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in a placebo-controlled clinical trial, weight gain ranged from 0.9 kg to 2.6 kg.[2]

References: 1. SEROQUEL® (quetiapine fumarate) Prescribing Information, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. **2.** Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997;42:233-246.

Seroquel®
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

AstraZeneca

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437
Wilmington DE 19850-5437

7/01 201644

Please see Prescribing Information in pocket of this brochure.

www.SEROQUEL.com

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

REDACTED

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL

EXHIBIT 42
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

REDACTED

Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>

Judith Owens
Ext: 24164
11F34 Mereside

From: Eriksson, Hans A
Sent: Monday, July 07, 2008 3:53 PM
To: Rak, Ihor W; O'Dowd, Liza
Subject: FW: Updated Discussion document for the 09July08 Seroquel Peds SERM

Attachments: Weight SERM 09 July 2008.doc

Ihor and Liza,

Hot off the press, additional material for SERM.

Hans

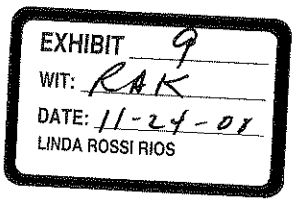
-----Original Message-----
From: Arnold, Karen
Sent: Monday, July 07, 2008 10:45 AM
To: Carey, Eileen; Dev, Vikram J; Arnold, Barry DC; Zander, Judith; Jefferies, Leigh; Leong, Ronald; Manning, Julia; Fors, Susanne (Seroquel); Boornazian, Lisa; Lee, Tara; Rolfe, Deborah; Warner, Linda (Safety); Delillio, Nina DH; Alam, Eva; Forsgren, Joachim; Spiers-Alston, Janet L; Gelman, Michele; Ni, Xiang; Eriksson, Hans A; Simpson, Brandon; Tyler, Robyn C; Åström, Mikael; Sherak, Nina; Walsh, Louisa M; Fullmer, Timothy S; Pathak, Sanjeev; Munro, Magna; Karlsson, Anders F; Patterson, Pat; Sullivan, Tim; Held, Peter; Stankowski, Jill; Nickless, Duncan M

Subject: Updated Discussion document for the 09July08 Seroquel Peds SERM

Dear all,

Additional data has been received for weight gain. An updated discussion document is attached. The new data is highlighted in yellow in the document.

Karen



AstraZeneca

Discussion Document

Drug name Quetiapine fumarate

Date *July 2008*

CONFIDENTIAL

Discussion Document

SEROQUEL/SEROQUEL XR AND WEIGHT GAIN

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

Author: Eva S. K. Alam, M.S., Pharm.D.
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE

Leigh Jefferies, MD
Global Safety Physician
Patient Safety, Wilmington, DE

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APPENDICES

SUMMARY

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the current clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not actual weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 2.10, 3.00). The incidence rate in patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

1. INTRODUCTION

The purpose of this document is to review relevant information such as, clinical study data, received by AstraZeneca regarding the association of weight gain in pediatric patients with SEROQUEL treatment and to assess whether the Core Data Sheet for SEROQUEL requires amendment to reflect the company's current understanding of the subject.

2. BACKGROUND

2.1 SEROQUEL / SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

It has been estimated that about 22.8 million patients worldwide have been exposed to SEROQUEL/SEROQUEL XR since launch through the end of February 2008. This estimate is based upon: (1) assumptions as to the number of prescriptions per patient, based upon 2007 United States (US) market research; and (2) projections of prescriptions since launch based upon information available in the US (dispensed prescriptions from retail, long-term care and mail order) and 12 other countries (Australia, Belgium, Canada, Egypt,Germany, Italy, Japan, Netherlands, Saudi Arabia, Spain, and United Kingdom; written prescriptions from office based physicians) in which SEROQUEL/SEROQUEL XR is marketed.

2.2 Core Data Sheet for SEROQUEL and SEROQUEL XR

The AstraZeneca CDS presents the company position on the prescribing information for SEROQUEL and provides a reference for consistency of product information documents in individual markets.

The current SEROQUEL/SEROQUEL XR Core Data Sheets contain the following information regarding weight gain in Section 4.8:

"As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with SEROQUEL".

Frequency	System Organ Class	Event
Common (≥ 1% - < 10%)	Investigations	Weight Gain[3]

[3] Occurs predominantly during the early weeks of treatment.

The current frequency of common is based on AE reports and not actual weight data.

3. THE LITERATURE

Not reviewed for this topic.

4. PRE-CLINICAL DATA

Not reviewed for this topic.

5. CLINICAL STUDY DATA

5.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer term open label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a breif description of these three trials.

- D144C00112: A 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D144C00149: A 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D144C00150: A 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.1 Acute placebo-controlled data

5.1.1.1 D144C00112

Adverse event data

Adverse events of weight increased were reported for three patients (4.12%) in the 400 mg/day mg/day quetiapine group, two patients (2.70 %) in the 800 mg/day quetiapine group, and two patients (2.66 %) in the placebo group. All adverse events of weight increased were judged related to the study medication by the investigator, and no adverse event of weight increased led to discontinuation of study treatment.

Mean increase in body weight

In study 112 mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥ 7% weight gain

A higher percentage of quetiapine treated patients (23.21 % in the 400 mg/day and 18.18 % in the 800 mg/day) had ≥ 7% weight gain at Day 42 compared to the placebo treated patients (6.82 %). (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.21)	10 (18.18)	3 (6.82)

5.1.1.2 D144C00149

Adverse event data

Adverse events of weight increased were reported for six patients (6.32 %) in the 400 mg/day quetiapine group, six patients (6.12 %) in the 600 mg/day quetiapine group, and none in the

placebo group. All adverse events of weight increased were judged related to study medication by the investigator and no adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine treated group, 1.7 kg in the 600 mg quetiapine treated group and 0.4 kg in placebo. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (See Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥ 7 % weight gain

A higher percentage of quetiapine treated patients (14.47 % in the 400 mg/day and 9.88 % in the 600 mg/day) had ≥ 7% weight gain at Day 21 compared to placebo treated patients (0 %). (See Table 4).

Table 4 D144C00149: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.47)	8 (9.88)	0 (0)

5.1.1.3 Pooled Data (Trials 112 and 149)

Adverse events of weight increase in pediatric studies D1441C00149 and D1441C0112 (pooled data)

In the pooled data, from the two acute placebo-controlled clinical trials (study 112 and study 149) with quetiapine in pediatric patients the incidence of reports of weight increased was 5.0 % in the quetiapine group and 1.2 % in the placebo group. The relative risk estimate (quetiapine vs placebo) was 4.13 (95% confidence interval: 0.96, 17.54). When adjusted for duration of exposure the incidence density for quetiapine was 64.8 per 100 patient years and 15.6 per 100 patient years for placebo. The relative incidence density was 4.17 (95% CI: 0.96, 18.03). (See Table 5).

Table 5 Number of patients with adverse events in pediatric studies D1441C00149 and D1441C00112

MedDRA preferred term	Treatment	Patients with event	Total patients[a]	Exposure[b]	Incidence rate[c]	Relative risk QTP vs Pla	95%CI Lower	Upper	Incidence density[d]	Relative incidence density QTP vs Pla	95%CI Lower	Upper
Weight increased	QTP	17 (0)	340	26.2 (27.0)	5.0 (0.0)	4.13	0.96	17.64	64.8 (0.0)	4.17	0.96	18.03
	Pla	2 (0)	165	12.9 (13.0)	1.2 (0.0)				15.6 (0.0)			

[a] Patients must have received at least one dose of trial medication.
[b] Exposure in patient-years, cencored at first event.
[c] 100xtotal number of patients with event/total number of patients.
[d] 100xtotal number of patients with event/total patient-years of exposure.
[e] The number of patients with any of the adverse events. Since a patient can have more than one adverse ecent within the adverse event group, the number does not necessarily equal the sum of the numbers below.

Note: Numbers outside brackets refer to all adverse events and numbers in brackets refer to serious adverse events.
Studies included: D1441C00149 and D1441C00112.
Derived from: Pgm: Reg-Def\Pediatric Apr08\...\AE_pla_ctrl. Data version: V15. User: Å Hellqvist. 07MAY08 14:20.

Patients with ≥ 7% weight gain by BMI (pooled data)

A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the majority of the different BMI categories (30.8 % vs. 9.5 % in the 0-<18.5; 18.6 % vs. 2.2 % in the 18.5 - <25; 5.2 % vs. 0% in the 25 - <30). A higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group ≤ 12 year old in the majority of the different BMI categories. (23.8% vs. 0 % in the 0-<18.5, 16.3 % vs. 0 % in 18.5 - <25). Similarly, a higher percentage of quetiapine treated patients had ≥ 7 % weight gain compared to placebo in the age group 13-18 year old in the majority of the different BMI categories (34.1 % vs.14.3 % in the 0-<18.5, 19.4 vs. 2.8 % in 18.5 - <25). (See Table 6).

Table 6 Patients with ≥ 7% weight gain by BMI in pediatric studies D144C00149 and D144C00112 (pooled data)

Weight Cut-offs	BMI group	PLA	All QTP	PLA ≤ 12	All QTP ≤ 12	PLA 13-18	All QTP 13-18
≥ 7 % increase at any visit		N n (%)	N n (%)	N n (%)	N n (%)	N n (%)	N n (%)
	0-<18.5	21 2 (9.5)	65 20 (30.8)	7 0 (0)	21 5 (23.8)	14 2 (14.3)	44 15 (34.1)
	18.5 - < 25	89 2 (2.2)	177 33 (18.6)	17 0 (0)	43 7 (16.3)	72 2 (2.8)	134 26 (19.4)
	25-<30	36 0 (0)	58 3 (5.2)	9 0 (0)	16 0 (0)	27 0 (0)	42 3 (7.1)
	30 - < 40	14 0 (0)	27 0 (0)	2 0 (0)	4 0 (0)	12 0 (0)	23 0 (0)
	≥ 40	2 0 (0)	2 0 (0)	0 0 (0)	0 0 (0)	2 0 (0)	2 0 (0)
	Total	163 4 (2.5)	335 57 (17.0)	36 0 (0)	85 12 (14.1)	127 4 (3.1)	250 45 (18)

Change from baseline in weight and BMI by BMI category (pooled data)

The pooled data for patients with a mean increase in weight and BMI from baseline to end of treatment were higher for quetiapine treated patients compared to placebo in each of the different BMI categories. (See Table 7).

Table 7 Change from baseline in weight and BMI by BMI category in pediatric studies D144C00149 and D144C00112 (pooled data)

BMI category (kg/m^2)		QTP		PLA	
	n	65		24	
Underweight BMI < 18.5		**Weight**	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	42.5 (7.5)	17.1 (1.2)	42.3 (10.2)	16.9 (1.2)
End of treatment	Mean (SD)	44.5 (7.9)	17.8 (1.5)	42.8 (10.0)	17.0 (1.3)
Change	Mean (SD)	2.0 (2.3)	0.7 (0.9)	0.5 (1.5)	0.2 (0.6)
Normal weight 18.5 ≤ BMI≤ 25	**n**	**181**		**90**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	57.1 (9.7)	21.5 (1.8)	58.3 (9.6)	21.6 (1.8)
End of treatment	Mean (SD)	58.9 (10.3)	22.0 (2.0)	58.6 (9.8)	21.7 (2.1)
Change	Mean (SD)	1.8 (2.4)	0.6 (0.9)	0.4 (2.5)	0.1 (0.9)
Overweight 25 ≤ BMI≤30	**n**	**60**		**33**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	72.4 (10.7)	27.4 (1.4)	69.5 (8.3)	26.8 (1.3)
End of treatment	Mean (SD)	73.5 (11.0)	27.7 (1.7)	68.8 (7.5)	26.4 (1.3)
Change	Mean (SD)	1.1 (2.6)	0.3 (1.0)	-0.8 (2.7)	-0.3 (0.9)
Obese BMI ≥ 30	**N**	**34**		**18**	
		Weight	**BMI**	**Weight**	**BMI**
Baseline	Mean (SD)	92.4 (14.5)	33.5 (3.1)	96.7 (11.3)	34.8 (3.6)
End of treatment	Mean (SD)	94.9 (16.7)	34.1 (3.4)	97.4 (12.5)	34.9 (3.9)
Change	Mean (SD)	2.5 (3.8)	0.7	0.7 (2.8)	0.1 (1.1)

5.1.2 Longer-term open label pediatric data

5.1.2.1 D1441C00150

Study 150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study 112) and in children and adolescents with bipolar I disorder (continuing from Study 149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Adverse event data

Adverse events of weight increased were reported for 51 patients (13.4%) in the safety population, including 24 patients (18.6%) who were treated with placebo during the acute feeder studies and 27 patients (10.8%) who received quetiapine during the acute feeder studies. Nearly all adverse events of weight increased were judged related to study medication by the investigator; three adverse events of weight increased led to discontinuation of study treatment.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 8.

The mean change in weight for all schizophrenia patients who enrolled from OL baseline to final visit was 3.3 kg; the increase in weight was greater in patients who were treated with placebo (4.3 kg) compared with quetiapine (2.8 kg) during the acute feeder study. The change in mean weight from DB baseline was 4.6 kg for schizophrenia patients.

The mean change in weight for all bipolar I disorder patients who enrolled from OL baseline to final visit was 4.0 kg; the increase in weight was greater in patients who were treated with placebo (5.5 kg) compared with quetiapine (3.2 kg) during the acute feeder study. The change in mean weight from DB baseline was 5.3 kg for bipolar I disorder patients.

The mean change in weight for all patients who enrolled in trial 150 (n=380) from OL baseline to final visit was 3.7 kg; the increase in weight was greater in patients who were treated with placebo (4.9 kg) compared with quetiapine (3.0 kg) during the acute feeder studies. The change in mean weight from DB baseline was 5.0 kg for the total population. The mean change in weight for patients (from OL baseline) who completed 26 weeks of treatment with quetiapine (n= 241) was 4.4 kg.

Table 8 Study 150: mean changes from baseline to the final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.34	113	64.8	19.18	175	65.7	18.22
Change from 112 DB BSLN	62	4.1	8.46	113	4.8	10.75	175	4.6	9.98
Change from 150 OL Baseline	62	4.3	6.90	113	2.8	10.07	175	3.3	9.08
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.85	136	64.5	18.43	200	65.8	19.61
Change from 149 DB BSLN	64	5.8	6.42	136	5.1	5.66	200	5.3	5.90
Change from 150 OL Baseline	64	5.5	5.81	135	3.2	4.75	199	4.0	5.21
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.26	249	64.7	18.74	375	65.7	18.95
Change from DB BSLN	126	5.0	7.50	249	5.0	8.34	375	5.0	8.06
Change from 150 OL Baseline	126	4.9	6.38	248	3.0	7.64	374	3.7	7.28

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial 150, the mean change in weight from baseline was 4.4 kg. In these patients, the average percentiles at baseline and 26 weeks, respectively, were 64.0% and 64.7% for weigh, 49.4% and 49.0% for height, and 66.3% and 67.7% for BMI.

Patients with ≥ 7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 9). The incidence of ≥7% weight gain was higher in patients who were treated with placebo (39.4%) compared with quetiapine (33.7%) during the acute feeder studies.

In the schizophrenia population, 29.1% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was similar in patients on quetiapine in the Study 150 who were treated with placebo (30.6%) compared with quetiapine (28.3%) during the acute feeder studies.

In the bipolar I disorder population, 41.3% of patients experienced ≥7% weight gain. The incidence of ≥7% weight gain was higher in patients on quetiapine in the Study 150 who were treated with placebo (47.7%) compared with quetiapine (38.2%) during the acute feeder studies.

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥ 7 % increase in weight from baseline.

Table 9 Study 150: Patients with ≥ 7% weight gain (Summary safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

5.1.3 Additional analysis of Pediatric data

5.1.3.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI) since in BMI, the weight is adjusted for height. (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z score taking into consideration the age and gender of the subject. Z scores are able to show how different a child's weight or BMI is from the average children with the same height. (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z score of 0.5 over any duration of time. (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the DB baseline for bipolar-I patients to the final visit and end of treatment are similar for the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores (for patients who enrolled in study 150) from the total DB baseline to the end of treatment and final visit were higher in the prior placebo group compared to the prior quetiapine group. (See Table 10).

The mean BMI Z-scores for each visit are plotted over time for the treatment of placebo, quetiapine and total for study 150 (See Appendix A).

Table 10 Study 150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.20	113	**-0.1**	1.40	175	**0.0**	1.34
Week 26	41	0.4	1.05	86	0.1	1.22	127	0.2	1.17
Final Visit	62	**0.5**	1.03	113	**0.2**	1.25	175	**0.3**	1.19
149 DB Baseline	67	**1.0**[a]	1.01	138	**0.9**[a]	1.06	205	**0.9**[a]	1.04
Week 26	37	1.2	0.97	77	1.2	0.96	114	1.2	0.96
Final Visit	63	**1.2**	0.95	135	**1.0**	1.03	198	**1.1**	1.00
DB Total Baseline	129	**0.6**	1.15	251	**0.4**	1.32	380	**0.5**	1.27
Week 26	78	0.8	1.08	163	0.6	1.22	241	0.7	1.18
Final Visit	125	**0.9**	1.04	248	**0.7**	1.21	373	**0.7**	1.16

[a] The mean BMI Z score at baseline is much higher for the 149 population

Schizophrenia patients with ≥ 0.5 shift in standardized BMI Z score

A higher percentage of quetiapine treated patients (15 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to placebo treated patients (3 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (27.4 % at the end of treatment) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (21 % at the end of treatment). (See Table 11).

A higher percentage of prior placebo treated patients, who enrolled in study 150, (24.2 % at EOT) vs. prior quetiapine treated patients (14.2 % at EOT) from the OL baseline for schizophrenia had ≥ 0.5 shift in standardized BMI Z score. (See Table 11).

Table 11 Patients with ≥ 0.5 shift in standardized BMI Z score in Study 112 and patients from study 112 extending into Study 150

Occurrence	Double blind Study 112		Study 112 to OL Study 150		
Time/baseline	All Quetiapine	Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment /DB	22/147 (15)	2/75 (3)	24/113 (21)[a]	17/62 (27.4)[a]	41/175 (23.4)[a]
End of Treatment /OL			16/113 (14.2)[b]	15/62 (24.2)[b]	31/175 (18)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150

Patients with ≥ 0.5 shift in standardized BMI Z score in Study 150 by indication

A higher percentage of schizophrenia patients, (who enrolled in study 150) treated with prior placebo (27.4 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.2 % at EOT) from the DB baseline of study 112. (See Table 12).

A higher percentage of schizophrenia patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (14.2 % at EOT) from the OL baseline. (See Table 12).

A similar percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (21.5 % at EOT) form the DB baseline of study 149 (See Table 12).

A higher percentage of bipolar patients (who enrolled in study 150) treated with prior placebo (19 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (8.3 % at EOT) form the OL baseline (See Table 12).

Table 12 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by indication

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Patients with ≥ 0.5 shift in standardized BMI z score in Study 150 by age group

A similar percentage of ≤ 12 years old patients (who enrolled in study 150) treated with prior placebo (28 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (25 % at EOT) from the DB baseline (See Table 13).

A higher percentage of ≤ 12 year old patients (who enrolled in study 150) treated with prior placebo (24 % at EOT) had ≥ 0.5 shift in standardized BMI Z-score compared to prior quetiapine treated patients (8.6 % at EOT) from the OL baseline (See Table 13).

A similar percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (22 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (20.1 % at EOT) from the DB baseline (See Table 13).

A higher percentage of 13-18 year old pediatric patients (who enrolled in study 150) treated with prior placebo (21 % at EOT) had ≥ 0.5 shift in standardized BMI Z score compared to prior quetiapine treated patients (11.7 % at EOT) from the OL baseline (See Table 13).

Table 13 Patients with ≥ 0.5 shift in BMI Z score in Study 150 by age group*

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.2 Adult clinical trial data

An analysis of SEROQUEL and long-term weight gain was performed. This retrospective study assessed the magnitude and pattern of weight change during long-term treatment with SEROQUEL. Analysis of data collected from patients with schizophrenia, who were treated with SEROQUEL in AstraZeneca clinical trials from July 1993 to May 1999, was performed.

Weight changes were analyzed in patients treated for 12 weeks (± 4 days), 52 weeks (±30 days), and 104 week (±45 days). To be eligible for inclusion in the analyses patients had to have weight measurements recorded at baseline, and at the relevant time points (12, 52, 104 weeks). The primary cohort was the 52-week group.

All concomitant medications were stopped before entry into the trials, but in some concomitant antipsychotic medication was permitted during the open-label extension phases. Data were analyzed for all patients receiving quetiapine, and for the subgroup of patients who received quetiapine monotherapy.

In total, 378 patients with schizophrenia had weight data available after treatment with quetiapine for 12 weeks; of these 340 received quetiapine Monotherapy. Mean (95% CI) weight gain was 1.46 (0.98, 1.95) kg for all patients and 1.48 (0.98, 1.99) kg for the monotherapy group. Median weight gain was 1.15 kg for all patients and 1.36 kg for the monotherapy group.

In total, 352 patients with schizophrenia had weight data available after treatment with quetiapine for 52 weeks; of these 297 received quetiapine Monotherapy. Mean (95% CI) weight gain was 3.19 (2.27, 4.11) kg for all patients and 3.59 (2.57, 4.61) kg for the Monotherapy group.

In total, 166 patients with schizophrenia had weight data available after treatment with quetiapine for 104 weeks; of these, 143 received quetiapine Monotherapy. Mean (95% CI) weight gain was 5.16 (3.62, 6.70) kg for all patients and 5.59 (3.98, 7.20) kg for the Monotherapy group. Median weight gain was 4.1 kg for all patients and 4.5 kg for the Monotherapy group.

Ninety-seven patients with schizophrenia had bodyweight data available at Weeks 12, 26, and 52. These data indicate that during one year of treatment with quetiapine, 69% of the total mean weight gain occurred within the first 12 weeks and 96% in the first 26 weeks. Similarly, data from the 12, 52, 104 week cohort (n = 5) indicated that 62% of the total weight gain occurred in the first 12 weeks of treatment. Furthermore, 99% of weight gain occurred in the first year, with negligible weight change between one and two years.

The results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia. Most weight gain occurs within the first 12 weeks of treatment and has no clear dose relationship. (Brecher et al 2007)

5.2.1 Acute placebo-controlled trials

The data below is taken from the cumulative clinical trial database (v15) for quetiapine. In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). (see Table 14).

The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 % (see Table 15).

Table 14 Incidence and relative incidence for weight gain risk, adult subjects – all Placebo-controlled trials

Risk	QTP incidence rate N=7481	Pla incidence rate N=3501	Relative incidence compared to Pla	Relative incidence 95% CIs	
	n (%)	n (%)	Ratio	Lower	Upper
Weight gain (> 7% increase)	721 (9.6)	134 (3.8)	2.5	2.1	3.0

CI Confidence interval. Pla Placebo. QTP Quetiapine.
Numbers in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Note: Trial D1448C00005, D1444C00004, D1447C00126, D1447C00144, D1448C00012 and D1447C00127 are excluded due to their initial uncontrolled open label phase prior to the randomised phase. Only the acute phase is included for trial D1447C00001and D1447C00134.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_pla_ctr.SAS. Programmer: F Strömberg. 2008-06-18 15:23. DB version: 15

Table 15 Incidence weight gain, adult subjects – all trials

Risk	QTP incidence rate N=22382
	n (%)
Weight gain (> 7% increase)	4070 (18.2)

Number in heading are patients with weight values at baseline and at least one value post baseline.
Note: Patients with multiple adverse events are counted only once.
Note: Percentages are calculated as (n/N)*100.
Program: Reg-Def\Prolactin May 08 MHRA\...\weigth_inc_all.SAS. Programmer: F Strömberg. 2008-06-26 9:14. DB version: 15

6. HOUSE SAFETY DATABASE OR POST-MARKETED USE

The post-marketing data was not reviewed for this topic.

7. DISCUSSION

Weight gain reported in pediatric patients taking SEROQUEL was identified as a subject for review by pharmacovigilance processes internal to AstraZeneca. In addition, we have reassesed the frequency of adult weight gain from the clincial trial data. The current Core Data Sheet reference to weight gain is based on adverse evnent report data and not acutal weight data.

In two acute placebo-controlled clinical trials with quetiapine in pediatric patients the incidence rate of patients with ≥ 7 % weight gain was 15.68 % respectively in the quetiapine group and 2.68 % in the placebo group. Using an increase of at least 0.5 standard deviation from baseline in BMI as a measure of clinically significant change, X% of patients on quetiapine met this criterion after 26 weeks of treatment.

In acute placebo-controlled trials of quetiapine in adult patients (≥18 years of age) the incidence rate in patients with ≥ 7 % weight gain was 9.6 % in the quetiapine group and 3.8 % in the placebo group. The relative risk estimate was 2.5 (95% CI: 3.00, 2.10). The incidence rate in adult patients with weight gain ≥ 7 % in all trials was 18.2 %.

The current Core Data Sheet refers to Weight Gain as common in Section 4.8 in the adult population, which is based on AE reports and not actual weight data.

Safety Evaluation and Review Meeting (SERM) is asked to consider whether the SEROQUEL CDS requires amendment with respect to the incidence of weight gain in pediatric and adult patients taking SEROQUEL.

8. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

Brecher et al 2007
Brecher M, Leong RW, Stening G, Osterling-Kiskinen L, Jones MA. Quetiapine and long-term weight change: A comprehensive data review of patients with schizophrenia. J Clin Psychiatry 2007; 68: 597-603.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 S-048

AstraZeneca Pharmaceuticals LP
Attention: Kathryn Bradley
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bradley:

We acknowledge receipt of your supplemental new drug application dated and received December 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets.

This "Changes Being Effected" supplemental new drug application provides for revised labeling to include new safety information for both adult and pediatric patients.

We have no objection to your submission of the new safety information pertaining to the clinical trials as a CBE supplement. However, the Division is requesting that you reformat the information for better integration in the overall label prior to your intended implementation on January 4, 2009. Specifically:

1. Place the pediatric safety information in the relevant sections of labeling with the adult data rather than separately in sections 5.19 and 8.4. For example, the proposed pediatric data in the section 8.4 subtitled "Changes in Thyroid Function Tests" should be placed at the end of section 5.10 (Warnings and Precautions: Hypothyroidism). The same principle applies to other pediatric safety information that already has adult data included prominently.
2. The weight gain signal is significant for both adult and pediatric populations and should be elevated to the Warnings and Precautions section rather than the vital signs section (the latter section could refer back to the information in Warnings and Precautions section) with inclusion of data for both populations. In fact, the data for weight change, glucose changes, and lipid changes from the clinical trials, both adult and pediatric, need to be elevated to the Warnings/Precautions section of labeling. Please see the format used in the currently distributed label for another antipsychotic drug, i.e., Zyprexa, for the correct format for this information.
3. The safety data for Increases in Blood Pressure is an unexpected signal and there is currently no similar adverse event signal for the adult population. Because of this unexpected and clinically significant signal that may be specific to the pediatric population, this safety data should be included in a separate section in Warnings and Precautions. Please offer your rationale for this unusual finding.

4. For each section describing pediatric safety signals, the following statement should be included "Safety and effectiveness of SEROQUEL have not been established in pediatric patients and SEROQUEL is not approved for patients under the age of 18 years".
5. Please replace your proposed Hyperprolactinemia statement with the standard language now used for more recently approved atypical antipsychotic agents, e.g., Invega. Any actual clinical trials data regarding prolactin elevation should, of course, be data for quetiapine, including the pediatric data.
6. All pediatric safety data and the other changes we are requesting for Seroquel should be included in revised labeling for Seroquel XR as well.

The above requested changes should be implemented immediately, and they should be submitted as an amendment to your pending supplemental application to the Seroquel NDA and as an original supplemental application to the Seroquel XR NDA, 22-047, within 30 days from the date of this letter, or notify FDA that you do not believe these changes are warranted, and submit a statement detailing the reasons. If you wish to have our prior comment on your alternative proposal in response to these requests, we would be happy to provide such comment.

Please note that your proposed labeling language in the above referenced CBE is under continuing review by the Agency. Please also note that the Division is currently reviewing your metabolic data submission and the pediatric efficacy supplements submitted under this NDA (S-045 and S-046). We will be providing further labeling comments, if any, and will take final action on these submissions when reviews are completed.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
12/18/2008 04:06:08 PM

EXHIBIT 33

Diabetes Information

Prevalence in the US population			
	General population	People with schizophrenia	People with bipolar disorder
diabetes	6%-7%[1,2]	13%[3]-18%[4]	10%[5]-26%[3]
smoking	34%-39%[6,7]	74%-90%[8]	35%*-55%[9,10]
obesity (BMI ≥ 30)	20%[2]-31%[11]	40%-60%[12]	30%[3]

*For mania

Testing and Monitoring Patients on Atypical Antipsychotics

- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness[13]
- ADA recommends that patients' weight be reassessed at 4, 8, and 12 weeks after starting on an atypical antipsychotic, and then quarterly during routine visits[14]

Patients Starting on an Atypical Antipsychotic[13]		
With an established diagnosis of diabetes	With risk factors for diabetes	Any patient
■ Monitor regularly for worsening of glucose control	■ Test fasting glucose at the start of treatment ■ Test fasting glucose periodically during treatment	■ Monitor for symptoms of hyperglycemia

Diabetes Risk Factors for Asymptomatic Adults[15]	
■ Age >45 years	■ Hypertension (BP ≥140/90 mmHg)
■ BMI >25 kg/m^2	■ HDL–C <35 mg/dL and/or triglycerides >250 mg/dL
■ Habitual physical inactivity	■ Polycystic ovary disease
■ First-degree relative with diabetes	■ IGT or IFG on previous testing
■ High-risk ethnic group (eg, African American, Latino, Native American, Asian American)	■ Other clinical conditions associated with insulin resistance (eg, acanthosis nigricans)
■ Having delivered a baby weighing >9 lb or having been diagnosed with gestational diabetes	■ History of vascular disease ■ History of smoking

See Important Safety Information on reverse side and accompanying full Prescribing Information.

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

Diabetes Information

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population[13]
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant[14]
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information[16]
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

Important Safety Information

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy with lithium or divalproex, and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL.

Precautions include the risk of seizures, orthostatic hypotension, and cataract development.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

See accompanying full Prescribing Information.

References: 1. CDC. National diabetes fact sheet. Available at: http://www.cdc.gov/diabetes/pubs/estimates.htm. Accessed April 7, 2005. 2. Mokdad AH, Bowman BA, Ford ES, et al. *JAMA*. 2001;286: 1195-1200. 3. Regenold WT, Thapar RK, Marano C, et al. *J Affect Disord*. 2002;70:19-26. 4. Bushe C, Holt R. *Br J Psychiatry*. 2004;184(suppl 47):s67-s71. 5. Cassidy F, et al. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry*. 1999;156:1417-1420. 6. Gopalaswamy AD. Smoking in chronic schizophrenia. *Br J Psychiatry*. 1986;149:523. 7. Masterson E, O'Shea B. Smoking and malignancy in schizophrenia, *Br J Psychiatry*. 1984.145:429-432. 8. Forchuk C. Schizophrenia and the motivation for smoking. Available on-line at: http://www.findarticles.com/p/articles/mi_qa3804/is_200204/ai_n9032259/print. Accessed on April 22, 2005. 9. Grant BF, et al. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2004;61:1107-1115. 10. Ucok A, et al. Cigarette smoking among patients with schizophrenia and bipolar disorders. *Psychiatry Clin Neurosci*. 2004;58:434–437. 11. AOA. AOA Fact Sheets: obesity in the U.S. Available on-line at: http://www.obesity.org/subs/fastfacts/obesity_US.shtml. Accessed May 2, 2005. Cigarette 12. Catapano L, Castle D. Obesity in schizophrenia: what can be done about it? *Australasian Psychiatry*. 2004;12:23-25. 13. SEROQUEL® (quetiapine fumarate) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2004. 14. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596-601. 15. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2005;28(suppl 1):S4-S36. 16. Data on file, DA-SER-30.

AstraZeneca

AstraZeneca Pharmaceuticals LP

Seroquel®
quetiapine fumarate
25 mg, 50 mg, 100 mg, 200 mg, 300 mg & 400 mg tablets

EXHIBIT 10

Unknown

From: Arvanitis Lisa LA
Sent: Wednesday, August 13, 1997 12:30 PM
To: Monyak John JT;Kowalcyk Barbara BB;Scott Mark MS
Cc: Griffett Christopher CR;RUHL Athena M. (MS Mail)
Subject: Weight gain

John, Barbara and Mark

I couldn't attend the Serebral meeting yesterday and haven't been able to catch up with anyone who had in order to hear what the discussion was opposite weight gain (I suspect no one had read the documents) but I did have a chance to look over John's document and have a couple of comments/thoughts. Perhaps we can chat afterward?

The purpose of this analysis is 2-fold:

1) Is there a competitive advantage for SEROQUEL re-weight gain which we can articulate in posters/talks/vis aids? We know we have weight gain but is it limited to the short-term treatment and flattens out over time? Clozapine continues to accumulate.
2) If not #1, then what do we tell the doctors when they ask about long term weight gain?

I recognize that there are a number of interactions/confounds in the analyses John did, but despite this I was really struck by how consistent the data was. Across pools (all trials, 15 alone, all trials - 15), across parameters/measures (mean change from baseline, %change from baseline, proportion with clinically significant weight gain), and across cohorts (various durations of treatment) the results seem to be consistent and show:

Weight gain is more rapid initially

While weight gain slows over the longer term (I only considered to 52 week) there still is weight gain. It doesn't stop...the slope just appears to change.

The magnitude of weight gain at 52 weeks (regardless of pool or cohort) is about 5 kg which is more than the short-term 6 week weight gain.

The proportion of patients with clinically significant weight gain at 52 weeks (regardless of pool or cohort) is about 45% and this is more than the % at 6 weeks.

This was quite surprising to me (not the weight gain but the consistency).

Therefore I'm not sure there is yet any type of competitive opportunity no matter how weak. Quantitative comparisons between compounds (clozapine, olanzapine) not from the same trials are seriously flawed. (Not that I would be giving up on an abstract but it requires more though before making a decision that this something we bally-hoo!) I have yet to re-check out the weight gain over time in the haloperidol group in 15 but comparisons here would be pretty shady!

The other issue of what we tell the sales force is more problematic because of the confounds. I feel the urge to delve more deeply into this but I realize resources are constrained, there are substantial limitations to the database and I'm not sure that the answers will be much different.

Thoughts are:

It appears on the scatterplot with slope marked that patients with lower body weights had a greater weight gain. (Note that Lilly has made this type of an argument stating that patients starting treatment at less than ideal body weight for frame size [they collect height information which we didn't] gained more weight. We can't draw these conclusions so convincingly.). Could the effect of sex be related to baseline weights of men and women? If I recall from CTRs, our women were generally heavier.

Could the interaction with age be confounded by sex or even baseline weight?

We know that weight gain is dose related. Does the fact that during the first 6 weeks of treatment in many trials many patients were on low doses and when they got into OLE they may have shifted the dose upward (OLE was flexibly dosed) and therefore delayed the appearance of weight gain appearing as an effect of time on drug? Would analysis of Study 14, the only trial with flexibly dosed acute treatment which offered long term OLE be of help here?

The effect of trial isn't surprising. Is it worth repooling like with like?
For example, perhaps looking just at Studies 12, 13 and 14 which are 6 week acute studies which offered OLE or adding Studies 6 and 8 as well since the populations were similar (Studies 5, 4, 15, 48 and the clin pharm studies with OLE could be argued as having different populations).

I have to keep asking myself, are we going to go through the motions, using precious resources and not really come up with anything more solid for the sales reps?

Comments? Thoughts? Shold we get together to chat?

Thanks
Lisa

EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE:

SEROQUEL PRODUCTS LIABILTY LITIGATION

CASE NO. 6:06-MD-01769-ACC-DAB

MDL DOCKET NO. 1769

May 28, 2008

Confidential Videotaped Oral Deposition of MARTIN BRECHER, M.D., D.M.Sc., MBA, held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, Philadelphia, Pennsylvania beginning at approximately 9:00 a.m., before Ann V. Kaufmann, a Registered Professional Reporter, Certified Realtime Reporter, Approved Reporter of the U.S. District Court, and a Notary Public.

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
Philadelphia, Pennsylvania 19103
877.370.3377

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merged entity for six to eight months when I joined.
Q. And you mentioned that Wayne Geller came over from Janssen a little bit after you; correct?
A. That's right.
Q. Was there any connection between you going to AstraZeneca and Dr. Geller going to AstraZeneca or was it coincidence?
A. I had given Wayne Geller's name to the director of safety as someone who was a good worker.
Q. Okay. So was he recruited to work at AstraZeneca because of your recommendation?
A. Possibly. I remember a conversation with Vikram Dev. I don't -- and I don't think I would have offered. I think, my best recollection, he would have asked, do you know. So it would have been along the lines, do you know any good safety people.
And assuming that was the

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question, I would have said, Yeah, Wayne Geller.
Q. Okay. You trusted his judgment?
A. Yes, I did.
Q. He wasn't fired from Janssen, was he?
A. No.
Q. When you started in December of 1999, did you take some period of time to educate yourself about Seroquel and what had happened previously?
A. I tried.
Q. Did you take a look at what studies were out there that had been done that were successful studies?
A. I remember reviewing the submissions to the FDA and the European countries.
Q. Okay. Did you review the studies that were failed studies?
A. I was aware of them.
Q. Okay. Did you review any

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cursed studies?
A. Sorry? Any?
Q. Cursed studies.
MR. McCONNELL: Objection to form.
A. I don't know any cursed studies.
Q. Okay. Do you know any studies that you reviewed where smoke and mirrors were used to present them?
MR. McCONNELL: Objection to form.
A. I don't -- I heard that expression in one context, I don't remember which, but that -- but certainly in my review of the documents when I joined the company, it did not include a reference to smoke and mirrors.
Q. Do you know about study 15?
A. Pardon?
Q. Do you know about study 15?
A. Yes.
Q. What was study 15?

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A. Study 15 was a long-term study comparing three doses of Seroquel to haloperidol for the prevention of relapse in schizophrenia.
Q. Okay. And when did you first become familiar with study 15?
A. I must have read about it in reviewing the submission documents to the FDA and the EEU because it was in the package.
Q. Okay. Did you ever review the weight gain data from study 15?
A. I can't say. I don't believe the weight gain -- I don't think there was a lot of weight gain data from study 15 because, as I understand now, only 28 patients actually completed a year of treatment.
Q. I'm going to show you what was previously marked as Schwartz Exhibit No. 41 and now is marked as Brecher Exhibit 3.
(Below-described document marked Brecher Exhibit 3.)

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BY MR. BLIZZARD:
Q. Do you see that this is an e-mail or an internal memorandum that's dated February 12, 1997?
MR. McCONNELL: Objection, foundation.
A. I'm sorry, your question again, please?
Q. Do you see this is an e-mail dated February 12, 1997? Actually, strike that.
Do you see this as an internal memorandum dated February 12, 1997?
A. Yes.
Q. It says here that it is from Richard Lawrence. Do you know who Richard Lawrence is?
A. I never met him, and his name has come up, but he was way before my time.
Q. Okay. Well, this looks like it's about almost three years before your time.

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A. That's right.
Q. It's regarding a U.S./Canada investigator meeting and study 15. Do you know anything about the U.S./Canada investigator meeting?
A. No.
Q. Did you review any of the that material when you came on board at AstraZeneca?
A. I don't recall ever seeing material specifically relating to the U.S./Canada investigator meeting.
Q. Do you see that this distribution of this e-mail went to Don Stribling?
A. Yes.
Q. Do you know who Don Stribling is?
A. I knew him when he worked in Japan. He once came to a meeting that we had with our Japanese collaborators. And he subsequently was the head of regulatory affairs.
Q. So he was pretty high up

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the corporate totem pole, wasn't he?
MR. McCONNELL: Objection to form.
A. I don't know what position he had in 1997.
Q. Well, when you knew him, he was fairly high up the corporate totem pole, wasn't he?
A. Yes.
MR. McCONNELL: Objection to form.
A. Yes. He was the --
Q. Let me try corporate ladder.
A. In his role as the head of regulatory affairs for the company, that's a responsible and senior position within the clinical development organization.
Q. Okay. Now, do you see in this -- first of all, that this was CC'd to a Lisa Arvanitis?
A. Yes.
Q. Do you see that? Do you

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know who Lisa Arvanitis is?
A. Lisa Arvanitis was the medical leader for Seroquel probably at the time of the writing of this e-mail. She had been gone from the company for some time when I arrived.
Q. So was she in your job as of the time of this e-mail?
A. To the extent -- I think she was the medical leader for Seroquel at the time. I think that's a fair guess on my part. Obviously I wasn't there, but I was aware that Lisa Arvanitis was leading the quetiapine effort, and so I think that she had a job roughly analogous to mine.
Q. Okay. Do you see where it says in the e-mail here that: "I am not 100% comfortable with this data being made publicly available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke and mirrors' job!" Do you see that?

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Q. Okay. So he wasn't happy, was he?
MR. McCONNELL: Objection to form.
A. Well, I think his e-mail speaks for itself. I think he was -- expressed concern, I would say. As he said he questioned the rationale for distributing it to the marketing people for, quote, informal review.
Q. And your response is to say I don't see a problem with marketing knowing where we're going; correct?
A. Yes.
Q. Were you trying to lobby the marketing people to support you in the decision to keep "limited" in the core data sheet?
A. I don't think that's where that e-mail is going at all. I think all I'm saying there is I didn't see a problem with marketing knowing what our position was. And that's what I said before, before you showed me this

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document, I said I didn't see a problem with the marketing people seeing the discussion documents prior to the meeting.
Q. Well, do you see a problem with soliciting their comments to the discussion document?
A. I think that this -- it would be inappropriate if a drug safety person would ask for marketing comments, and I don't think that ever happened. This --
Q. Well, you were -- I'm sorry. Go ahead.
A. This discussion document, as I said, immediately after you showed it to me, is unusual in that it's being produced by a member of the Seroquel team. And I have offered a possible explanation why. And clearly the writer wanted to get marketing's view on the content.
Q. Well, did you -- you were on the e-mail that was sent by Emma

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Witch soliciting comments of the marketing folks and others; correct?
A. Yes.
Q. Okay. Did you say "Whoa, Emma, don't go submitting this for comment to the marketing people"?
A. I did not.
Q. Did you tell her in any way that she should hold off sending this to marketing for comment because it was inappropriate?
A. I did not.
Q. Now, the discussion -- the SERM meeting that occurred in June of 2000, did you attend that in person?
A. The June 2000 SERM, yes.
Q. Where did it occur?
A. It must have occurred in Wilmington.
Q. Okay. But you specifically have a memory of being there for the meeting?
A. Not a strong one. You know, it's clear from the earlier

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document that you showed me that I was there. And I don't have a vivid recollection of the meeting, but I do have a recollection of being there.
(Below-described document marked Brecher Exhibit 18.)
BY MR. BLIZZARD:
Q. I have handed you Exhibit No. 18, and it has a number of handwritten notes on it. Are those -- is that your handwriting?
A. Yes.
(Below-described document marked Brecher Exhibit 19.)
BY MR. BLIZZARD:
Q. Before I get to what that says, let me mark as Exhibit 19 to your deposition -- are these draft minutes of a meeting in July of 2000?
A. This is -- are you talking about 19?
Q. Yes.
A. They are draft minutes.
Q. Okay. Is that a -- are the

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minutes prepared by Emma Witch?
A. Yes.
Q. And is Emma Witch shown as an attendee at this meeting?
A. Yes.
Q. Are these other people involved in this meeting, SERM members?
A. Wayne is a SERM member. I don't know whether or not Paul Duffy would have participated in SERM. He was a -- he is a toxicologist and was involved in the preclinical work with Seroquel.
Q. Okay. So these meeting minutes do not reflect the minutes of SERM, do they?
A. No.
Q. Okay. This is a separate meeting that relates to the preparation of the FDA response to the -- on the diabetes issue?
A. Response to the FDA, right.
Q. Okay. Well, we will get to that in a minute then.

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Take a look at the discussion document for Seroquel. These handwritten notes that were made on this document, Exhibit 18, were -- when were those made?
A. You know, I'm not sure what document this is. I can guess, but perhaps you could tell me.
Q. Well, as the title says, "Diabetes Mellitis, Diabetic Ketoacidosis, Non-Ketotic Hyperosmolar Coma, and Hyperglycaemia." And it is a discussion document regarding Seroquel; correct?
A. Yes.
Q. And it's prepared by Wayne Geller; correct?
A. Yes.
Q. I believe that this document was prepared in advance of the SERM meeting and was discussed at the SERM meeting. That's my belief. Do you recall that?
A. Are you referring to the

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June 2000 SERM meeting?
Q. Yes.
A. That's what I think as well. I just don't see a date on this document. But looking at the cover and just quickly glancing through the interior, I think this is the discussion document or a draft of it prepared for this -- as a discussion document for the June 2000 SERM.
Q. Okay. What I would like for you to do for me is to read your handwriting. Sometimes I can read it; sometimes I can't. And I want to make sure we have an accurate rendition of your handwritten notes from this meeting.
First, on the first page at the top, what does that say?
A. Where it says 1)?
Q. Yes.
A. That's angioedema.
Q. What have you crossed through at 2)?

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A. I think it's -- "limited" is crossed out.
Q. Okay. What's No. 3)?
A. It looks like "hyperglycemia" and "diabetes."
Q. Okay. Do you know why "limited" is crossed out in No. 2)?
A. I can't recall.
Q. Is it possible it relates to the weight gain issue?
A. I have no recollection what I was thinking when I wrote these notes.
Q. Okay. So all you can do at this point is read them to me; correct?
A. That's right.
Q. Okay. What does the note on the right-hand margin say that says "OS"?
A. I think that's "US."
Q. Okay.
A. That makes more sense to me. And I think to the right of that it says "involuntary movements."
Q. Okay. And then it says

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"CDS"?
A. "Discussion."
Q. What does "CDS" stand for?
A. Core data sheet.
Q. Okay. Then on the first page out on the left-hand side under the heading "All Findings Presented in This Document Are to Be Subject to Further Consideration at SERM," does it say "6 cases"?
A. Yes.
Q. What does it say beneath that?
A. Below that?
Q. Yes.
A. I can't make out the first word. And then it says "time to onset new diabetes 0.5 months." Oh, "Median." "Median time to new onset diabetes 0.5 months."
Q. Okay. And then in the middle of that, just to the right of that note, what does that say? It says "Wayne" at the top and that is

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underlined?
A. Yeah. "Page 8, 2240 base rates." And then it says something that doesn't make sense to me, gdv or gov. I don't know what that means --
Q. Okay.
A. -- with a question mark.
Q. And then over on the right-hand margin, what does that say?
A. "Emma, MJ - dose response." MJ would be Martin Jones. And then below that --
Q. Is Emma Emma Witch?
A. Probably. I think that we also had an Emma Westhead, but -- so I don't know which Emma this is referring to.
Q. Okay.
A. And then "Geert - 6 cases, conclusions."
Q. So what does "Geert" refer to?
A. Geert would refer to Geert deVriese, who was the global product

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director.
Q. Okay. Do you know what the "6 cases" references?
A. You know, I don't know if it's the same six cases referred to on the left.
Q. Okay. And what does it say beneath that? There's an arrow pointing down.
A. I can't quite read the first word. And then the second word is "CDS in line with US PI?" Oh, "bring." I think it says "Bring CDS in line with US PI?"
Q. Okay. So there was some question about whether -- or somebody was raising the question of whether the CDS should be brought in line with the U.S. package insert; correct?
A. I don't know if that was my question or someone else's question.
Q. Okay. And then underneath that what does it say?
A. "Conclusion: Keep issue

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under review."
Q. And then under -- on the bottom of the page what does it say?
A. "Of 10 cases from clinical trials," arrow "each source?"
Q. Second page up at the top?
A. "RIS labelled for diabetes, DKA."
Q. And that's diabetic ketoacidosis?
A. That's what the DKA would stand for.
Q. Okay. Under -- right next to the "Introduction" section, what does that say?
A. "Criteria used in this assessment." It looks like "FBS," which would be fasting blood sugar, "greater than 126 2 hour post, 75 grams greater than 200."
Q. Okay. Can you interpret that note?
A. Yeah. I think that -- what I think it means, without confirming it

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from the text, is that the criteria used in the assessment was either a fasting blood sugar greater than 126 or a two-hour glucose value following 75 grams of glucose -- in other words, a glucose tolerance test -- with a value greater than 200.

Q. Okay. If you go turn the page to the next note that we have. It looks like it's over on Page 6.

Okay. What does that say?

A. On the top?

Q. Yes.

A. "No attribution." And then to the right of that it says "16, SPONT," probably referring to -- standing for spontaneous; "10 clinical" -- "10 CLIN trials," referring to ten clinical trials; and "2 lit reports." So what this is referring to is 16 spontaneous reported adverse events, ten clinical trial reports, and two reports in the literature, and they are pointing to no attribution.

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Q. Okay. Under "CLINTRACE Database (In House Safety Data)," there's a note that says "9 cases"?

A. "9 cases new onset, 4 DKA, 2 new onset, 2 worsening." And then below that is "NKHOC-0." And NKHOC would stand for nonketotic hyperosmolar coma.

Q. And then you've got a star next to this particular description of this event of a 43-year-old male with a history of mental illness who developed new onset diabetes. Do you see that?

A. Yes.

Q. Do you know why it was starred?

A. No. And I'm just curious whether I starred other cases.

Q. I think you did. Look over at the next page. Do you see that?

A. Yes.

Q. And this particular case is a diabetes case with weight gain; correct?

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A. Yes.

Q. And you starred that?

A. Yes.

Q. And do you know why you starred it?

A. No.

Q. I assume that you starred things that were important to you; is that correct?

A. Presumably. I certainly don't -- I'd have to pore over this document to see what were the common features of the starred cases. I don't recall that now.

Q. Okay. Look over at the next page. Do you see that there's a starred event on this page as well?

A. Yes.

Q. And the next page, "Loss of Diabetic Control, Tooth Pain, Insomnia"?

A. Yes.

Q. Do you see that that event is starred?

A. Yes.

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Q. If you look over at Page 11 --

A. Yes.

Q. -- do you see a star there?

A. Yes.

Q. Do you know anything about why that star is there?

A. I don't recall the principle leading to the starring of cases.

Q. Okay. If you look over on Page 15, there's a star next to another case of hyperglycemia?

A. Yes.

Q. Okay. On Page 16 --

A. Yes.

Q. -- could you read that handwriting for us?

A. It says "Median?" Below that "time to onset." There's text that reads "The former patient reportedly lost 30 pounds," and then there's a line from that going to a handwritten note saying "Type 1 - pattern."

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Below that it says "2 cases of DKA - weight gain associated." And then below that there's a -- it says "criteria greater than 110" -- it looks like greater than 110 pounds, but I'm not sure what that means.

Q. This relates to reports of hyperglycemia.

A. Oh, I'm sorry. I can -- this one on Page 16 on the bottom that the arrow says "criteria greater than 110 fbs," it's for fasting blood sugar.

Q. Okay. And the last page, Page 17, what does the note at the top say?

A. "Note, Wayne impressed by 2 physicians noting diabetes onset with dose increase."

Q. Okay. So does that note reflect that Dr. Geller was impressed with the dose-response?

A. I don't think that represents a dose-response so much as exactly what it says, that two

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physicians noted diabetes onset following a dose increase. I don't think that indicates a dose-response.

Q. It indicates that the diabetes onset occurred after the dose was increased; right?

A. That's right. It is different from a dose-response.

Q. Okay. The next item in the middle of the page says what?

A. "Usually no baseline blood glucose. 7 taking drugs associated with diabetes. Some reports - scant information" -- "scant inf" meaning scant information -- "no positive de," which means no positive dechallenge or rechallenge.

Q. What's the next note say?

A. "Seroquel may cause impaired glucose regulation in some individuals. No signal of Type 1 ie no negative impact on insulin production."

Q. Okay.

A. Well, that -- "Discussion:

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No positive re,de challenge. No baseline CHO," referring to no baseline glucose. "Low number of cases for a common condition."

That's actually an important point because diabetes is very common. And my comment here, I think, reflects the view that this is a small number of cases for an illness as common as diabetes, given the exposure that we had by 2000.

"No mechanism of effect."

On the right it says "For my part only 4 cases of DKA speaks to absence of diabetogenic effect."

Below that: "Other patients: 1., will get long term data from olanz trial. 2., will" --

Q. What's "olanz trial"?

A. That would refer to olanzapine, but I'm not -- I don't know what olanzapine trial I was referring to, unless -- probably given that it was 2000, it could either have referred to

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the long-term trials that Lilly conducted or to the long-term trial that Janssen conducted.

And then below that, "will" --

Q. "Know more?"

A. "Will" --

Q. -- "know more after response to FDA concludes."

A. I think so.

Q. I may have stared at it longer than you, so whatever you need to do to confirm it.

A. Yeah, I think that's right.

Q. Okay. So in looking at this, you made the -- when you started talking about this discussion down here below the line, you may have said, well, here are a couple of important points.

And then there's these comments above the line that you read without making a comment about it.

Is it your memory, from looking at this now, that the points

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metabolism disorders. Dear Wayne, thank you for yoy fax" -- I guess that is supposed to be "your fax" -- "which I sent to the local authorities."
A. Yes.
Q. And when he actually faxed it to her, if you look at the -- Geller's communication on Page 2, do you see where he says: "Hi, Dorothee. The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once." Do you see that?
A. Yes.
Q. And then she sends back and says thanks for the fax; correct?
A. Yes.
Q. Okay. So, again, Dr. Geller is offering to sign this document before faxing it; right?
MR. McCONNELL: Objection to form.
BY MR. BLIZZARD:

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Q. Let me rephrase that. Dr. Geller is offering to sign the document that was attached; right?
MR. McCONNELL: Same objection.
A. Wayne is offering to sign the document.
Q. Right. and would that indicate to you, as a reasonable person who conducts business in the way that people typically conduct business, that that is not a draft?
MR. McCONNELL: Objection to form.
A. I was not involved with this correspondence between the Dutch and Wayne. And if Wayne was mistaken about his document, I don't think it matters whether or not he signed it or not. I don't know whether he knew it was a draft or not. And I can't comment. I just don't know his procedures well enough to comment on what's the implication of signing the

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document.
Q. What is the implication when you sign a document?
MR. McCONNELL: Objection to form.
A. When I sign a document, I usually -- it means that I wrote this document.
Q. It means you are taking responsibility for what's in the document; right?
A. Usually.
Q. And that's what it would mean here, wouldn't it, that he was taking responsibility as a global drug safety physician for the statements made in the document?
A. I want to say --
MR. McCONNELL: Excuse me. Objection to form.
A. I want to say two things: I don't know what Wayne -- was going through Wayne's mind and I don't want to comment on what it meant that he signed

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this document.
Moreover, if we get back to the document, I just don't feel that the arguments and the data that are in the document, particularly in the executive summary, are supporting the conclusions. So -- but, regardless, I don't think that -- I just can't comment -- I don't know whether this was the document that was mistakenly sent and I don't know --
Q. How do you --
A. I can't comment on the interaction between Wayne and the Dutch authorities because I was not involved in that transaction.
Q. Well, the e-mail that we just reviewed clearly indicates that the Dutch authorities were asking for an analysis of glucose metabolism and Seroquel; correct?
MR. McCONNELL: Objection to form.
A. The Dutch wanted a review

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of cases or an analysis of cases of diabetes and glucose metabolism that may or may not have been related to Seroquel.

Q. Right. And people within the marketing company over in the Netherlands asked Wayne Geller to submit a paper, and he offered to sign and faxed this safety position paper to them; correct?

MR. McCONNELL: Objection to form.

A. Wayne attempted to be responsive to a request and offered to sign a document.

Q. Now, the Dutch authorities weren't just acting as a single country in Europe at the time with respect to Seroquel, were they?

A. The Dutch was a reference member state.

Q. And the reference member state takes the lead for the entire European Union with respect to a

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particular drug that they are the reference member state for; right?

A. Right, for those states participating in the process.

Q. Okay. Do you know how many states in the European Union were participating in the process at the time in 2000 when this paper was sent to the Dutch authorities?

A. Well, account -- you know, there were new countries that joined the European Union over time, so I don't recall how many were there in 2000.

What I do know is that France was not a part of it and we had a separate registration procedure in England and Italy. So that the reference member state would have -- or that role as reference member state would have applied to the other Western European countries.

Q. Okay. Now, this document that we just read the conclusion of that was submitted to the Dutch, assuming it

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was the one that was submitted to the Dutch, that contained markedly different conclusions than the one that was given to the FDA, didn't it?

A. Well, I don't think I've looked at the FDA position paper today. And I think the position stated here is at variance with the FDA position paper.

Q. Okay. Well, we can look at the FDA position paper, and we will probably do that tomorrow. But I mean, without reading it, you know that the company did not write a paper to the FDA saying that there's reasonable evidence to -- that Seroquel can cause diabetes or hyperglycemia in certain individuals?

A. That's right.

Q. Right. In fact, you never sent this safety position paper of Dr. Geller to the FDA, did you?

MR. McCONNELL: Objection to form.

A. I don't think this safety position paper was sent to the FDA.

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Q. Right. Even today FDA doesn't have this safety position paper, does it?

A. And I don't think that this represents the view of AstraZeneca or the drug safety department at that time or, for that matter, now.

MR. BLIZZARD: Objection, nonresponsive.

BY MR. BLIZZARD:

Q. Now, let me ask you something that's really on a different subject now, and I think with that I'd like to maybe conclude for the day and we will save some additional time for tomorrow.

After the SERM meeting in 2007 there was a discussion document that was actually presented at the SERM meeting. And I have a copy of it. I'm not going to attach it today, but I think it's about 500 pages long. Do you recall that document?

A. It was a long discussion

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Q. Do marketing and commercial people at AstraZeneca have any role whatsoever in the SERM process?
A. They do not.
Q. Doctor, as part of the preparation for SERM, is safety data review and analyzed?
A. Yes.
Q. Could you explain to the jury what type of data is reviewed and analyzed as part of the SERM process?
A. The SERM reviews should include, and typically do include, the data from clinical trials, postmarketing surveillance and literature reviews, and sometimes the preclinical data as well.
Q. Is material from the global drug safety database reviewed as part of the SERM process?
A. Yes.
Q. Doctor, did AstraZeneca create the SERM process specifically to examine the glucose issue relating to Seroquel?

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A. Yes.
Q. They did that in the spring of 2000?
A. The SERM meeting for glucose was in June of 2000.
Q. Okay. Does AstraZeneca also use the SERM process at times for other drugs involving other issues?
A. The SERM process is used for all drugs, all marketed drugs at AstraZeneca.
Q. Does AstraZeneca convene SERMs only to respond to FDA requests?
A. No.
Q. In your experience, is the SERM process an effective tool to monitor the safety of the drug?
A. Yes.
Q. Why?
A. The SERM -- a SERM meeting is called whenever a question or an issue is raised around the safety of marketed medicine. So that could happen whether concerns are raised from within the

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company or in response to a request from a regulatory agency.
Q. Does the SERM process play a role in determining whether the core data sheet should be changed?
A. Yes.
Q. What is the core data sheet?
A. The core data sheet is the best description of the safety profile of the drug and represents the core items that have to be included in every product label. So it's that -- those facts about the safety of the drug that must be included in every label around the world.
Q. When AstraZeneca does convene a SERM, does the SERM always conclude that the core data sheet should be changed?
A. No, it doesn't.
Q. Does the SERM always conclude that the core data sheet should not be changed?
A. No, it doesn't.
Q. What explains the difference

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in those different kinds of decisions?
A. The critical point is whether the label accurately reflects the safety profile of the drug as we understand it.
Q. Does the SERM decision as to whether or not to change the core data sheet depend in any way upon the available data?
A. The SERM decision to change the core data sheet depends entirely on the data.
Q. Is the SERM process the only way that AstraZeneca monitors the safety of Seroquel?
A. No.
Q. What other procedures are in place at AstraZeneca to monitor the safety of Seroquel?
A. The drug safety department is monitoring safety on a continuous basis. And so are the clinical trials people. Clinical trials people are monitoring safety as the clinical trials

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are ongoing.
Q. Does anyone or any department at AstraZeneca monitor adverse events?
A. Primarily drug safety and also the clinical group.
Q. Does AstraZeneca submit periodic safety updates to the FDA?
A. Yes.
Q. In your experience, did AstraZeneca closely monitor the safety of Seroquel?
A. Yes.
Q. Now, you've discussed the SERM process generally. Are there documents that are associated with the SERM process?
A. Yes. Prior to a SERM meeting there's a discussion document. Following the SERM meeting there is either a position paper or justification document that's prepared.
Q. What's the purpose of a discussion document for SERM?

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A. A discussion document is written so as to inform the discussions at SERM of all the relevant facts.
Q. What's the purpose of a SERM position paper?
A. A SERM position paper is that -- is a paper that is written after a SERM meeting when the core data sheet is not changed on a particular issue. And it reflects the reasoning as to why the core data sheet is not changed on that point.
Q. Now, we talked about the FDA request in May of 2000 regarding glucose data. Did you participate in a SERM in 2000 regarding glucose issues?
A. Yes.
Q. Was there, in fact, a discussion at AstraZeneca at the SERM regarding glucose data?
A. Yes.
Q. What did that SERM conclude regarding whether there was reasonable evidence of an association between

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Seroquel and hyperglycemia or diabetes?
A. SERM decided to keep those issues under review, but not to change the core data sheet.
Q. What did SERM conclude as to whether there was a causal link between Seroquel and hyperglycemia or diabetes?
A. SERM did not conclude that there was a causal link between Seroquel and hyperglycemia or diabetes.
Q. What did SERM conclude in 2000 as to whether the data demonstrated reasonable evidence of an association between Seroquel and hyperglycemia or diabetes?
A. SERM concluded that the data did not show a reasonable evidence of an association.
Q. I want you to take a look at a document that the plaintiffs' lawyers put in front of you. It's Exhibit 18. Could we get a look at that?
Doctor, first of all, do you remember taking a look at Exhibit 18, I

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don't know if it was yesterday or the day -- I think it was the day before yesterday?
A. Yes, I remember.
Q. Could you turn to the last page, please?
A. Yes.
Q. Do you see handwritten notes on that page?
A. Yes.
Q. And that's your handwriting. Is that right?
A. Yes.
Q. I want to direct your attention to the handwritten notes that are underneath the typed section of the page. Do you see what I'm talking about?
A. Yes.
Q. All right. Do you recall testifying on Wednesday that those notes were your reflections on reading the document?
A. Yes.
Q. I want to get you to focus

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questions now about another trial, it's one that you've been asked some questions about. I want to give you an opportunity to describe it to the jury. That's trial 125. Were you involved with trial 125?

A. Yes.

Q. Could you explain to the jury what trial 125 is?

A. Trial 125 was an effort by AstraZeneca to understand the effects of Seroquel on glucose metabolism. And to do that we used a more sensitive assay even -- than even the fasting glucose. We used the glucose tolerance test. That's very important because the glucose tolerance test becomes abnormal earlier in the course of diabetes than the fasting blood sugar so it was a sensitive test for the emergence of diabetes. We --

Q. Would it be -- I'm sorry, keep going.

A. We measured the area under the curve for the two hours of the

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glucose tolerance test, and that, too, is a sensitive measure of whether there's an effect of a drug on glucose regulation. That was -- that's one important point.

The second important point was that we hospitalize the patients overnight both at baseline at week 12 and at week 24. And, therefore, we could be sure or as sure as one could reasonable want that the patients had not eaten prior to the exam both at baseline and at week 24.

Third, we were able to find patients who had not been previously exposed to atypical antipsychotics, so we were measuring -- we were studying relatively naive patients, and so we were able to look at results independent of what the patients had been on before. And lastly, the study was a long study, it was 24 weeks, and so we were able to have a good assessment of what the prolonged effect of treatment was on patients' glucose metabolism.

Page 1017

Q. Would it be absolutely accurate to describe trial 125 as a diabetes study?

A. No, it was not a diabetes study. It was an attempt to look at the effects of Seroquel on glucose metabolism measured by the two-hour glucose tolerance test.

Q. I just asked you about whether you can call 125 a diabetes study. Are there any ethical constraints to conducting a study that a scientist would actually be able to call a diabetes study?

A. I think it will depend on the design. There are a lot of different design possibilities, and one -- it would depend -- you know, ethical issues in the study would depend on what was actually being done. One point about this study was that every patient received active medication. We could not use a placebo in this trial because it would have been unethical to deprive patients of

Page 1018

medication for 24 weeks.

Q. Did the FDA or any other government body require AstraZeneca to conduct trial 125?

A. This was done on our initiative.

Q. When did AstraZeneca decide to start designing and planning trial 125?

A. The decision to conduct that trial was made in November 2002.

Q. Why then?

A. That was shortly after we had received a strong label change in Japan and -- requiring us to provide warnings and I believe a contraindication for the use of Seroquel in patients with diabetes. And we recognized that we did not have sufficient data to address concerns that other regulatory agencies might have, and, therefore, we wanted to collect data that could establish, as best we could, the fact that Seroquel did not cause diabetes or it is not

Page 1019

associated with glucose metabolism. And conversely, if Seroquel was associated with disorders of glucose metabolism, we wanted to know and we wanted to have the data in which to -- to be sure that that was the case so we could write the label accordingly.

Q. Why did AstraZeneca include Risperdal in trial 125?

A. We wanted to compare Seroquel to the two other comparators -- to two competitors on the market. We wanted to make sure that everybody got medication. The study was, therefore, able to compare all three drugs for their effects on glucose metabolism. And the study was able to look at the effects on each drug relative to the others as well as the change in each drug compared to baseline.

Q. Why didn't AstraZeneca start planning trial 125 prior to the year 2002?

A. We -- prior to the Japanese

Page 1020

action, we thought that our -- that the data that we had gathered, particularly the summary prepared for the FDA in August of 2000, had established that Seroquel was not associated with diabetes or abnormalities in glucose metabolism.

The Japanese regulatory action made it clear that our data was not persuasive, at least to them, and so we wanted to do two things as I just said, gather data that would allow us to persuade another regulatory agency that might have had a concern; or conversely, if there was than effect of Seroquel on glucose metabolism, we wanted to show and demonstrate it to ourselves.

Q. Prior to the planning of trial 125, in your mind, had the preclinical and clinical studies that supported the FDA initial approval of Seroquel revealed any evidence that Seroquel could cause glucose dysregulation?

A. The evidence that we had at

Page 1021

that time did not show -- did not provide any evidence that Seroquel caused diabetes or abnormalities in glucose regulation.

Q. Prior to the planning of trial 125, did the postmarketing surveillance data reveal evidence of a causal link between Seroquel and diabetes or hyperglycemia?

MR. PIRTLE: Leading.

THE WITNESS: The postmarketing data did not provide data showing a causal link between Seroquel and diabetes.

BY MR. McCONNELL:

Q. At the time that you started planning trial 125 in the fall of 2002, were you aware of any trial like it that any company had ever done?

A. I was not aware of any such trial. I thought this was innovative on our part.

Q. And in terms of numbers of patients, was trial 125 a large clinical

Page 1022

trial?

A. Yes. We enrolled 500 patients, a little over 500 patients, and that's a moderate to large size trial, especially for one that's going for 24 weeks.

Q. Did AstraZeneca consult with outside experts on the design of trial 125?

A. I believe so.

Q. Who did you consult with?

A. I'm not sure. I don't recall precisely who we consulted with. Probably -- I think we consulted with Woolf and Goldstein. I don't recall for sure. Possibly consulted with John Newcomer. Again, I don't recall for sure.

Q. Does it take a long time to get a trial --

A. Let me finish.

Q. I'm sorry, go ahead.

A. We probably also consulted with endocrinologists within the company.

Page 1031

A. That result is an important one. The primary result of the trial as stated in the protocol was the area under the curve from zero to two hours of the glucose -- of the glucose values following the ingestion of 75 grams of glucose. And what you can see in Table S4 is that the change from baseline for Seroquel was not statistically significant at week 24 compared to baseline, while the change from baseline from both olanzapine and risperidone was statistically significant.

So in terms of the area under the curve of the glucose tolerance test, both olanzapine and risperidone showed a statistically significant worsening, whereas quetiapine did not.

Also in Table S5 when you compare the change from baseline in the area under the curve, the difference between quetiapine and olanzapine was statistically significant, obviously olanzapine was worse, and the

Page 1032

olanzapine-quetiapine difference was statistically significant in favor of quetiapine. The difference between quetiapine and risperidone was not statistically significant.

Q. At week 24, can you tell if there was a -- what sort of increase, if any, there was from baseline and fasting glucose for people who were using quetiapine?

A. We have to go -- it's not here. That -- the answer to that question I don't think is in the summary. I'm going to have to go into the body of the document to find that.

MR. McCONNELL: Go off the record for a second.

VIDEOGRAPHER: Off the record at 2:41.

- - -

(A recess was taken from 2:41 p.m. to 2:52 p.m.)

- - -

VIDEOGRAPHER: The beginning

Page 1033

of tape number four. We're back on the record at 2:52.

BY MR. McCONNELL:

Q. Doctor, did you manage to find the fasting glucose results for Seroquel?

A. Yes.

Q. What were the results?

A. The change from base --

MR. PIRTLE: Could you point me to the page? It's a big document.

THE WITNESS: Page 156. The change at week 24 in the quetiapine group was .177 millimeters per liter.

BY MR. McCONNELL:

Q. In the context of all the results of trial 125, did you find the results reassuring or not in terms of whether there was a connection between Seroquel and glucose dysregulation?

A. We found it very reassuring.

Q. Why is that?

Page 1034

A. Because the change in the area under the curve, which is the primary assessment, was not -- did not change significantly between baseline in week 24, and also because there was no change at all in the two-hour value, that is the blood glucose value two hours after glucose challenge showed no change. That value typically begins to go up as diabetes emerges. And the fact that there was no change in that value after 24 weeks on Seroquel was also reassuring.

Q. Doctor, I want to direct your attention to other studies now, studies 126 and 127. My first question to you is, did AstraZeneca collect fasting glucose samples in trials 126 and 127?

A. We attempted to and we also -- and we collected the time since the last meal, which will enable us to ascertain whether -- reasonably ascertain whether the sample was fasted or not.

Q. Can you explain to the jury

Page 1035

what it was that was studied in trials 126 and 127?
A. Trials 126 and 127 were designed to show that Seroquel could prevent relapse in patients with bipolar disorder. It was a complicated trial insofar as we studied patients who either -- had recently had or were having either a manic episode or an episode of depression and who had recovered on Seroquel and the mood stabilizer. And then we randomly assigned patients to continue on the combination or on the mood stabilizer alone. It was a -- it took a long time to recruit the number of patients. And it was a long time to accumulate the number of relapses. And we conducted that study twice in order to be sure of the result.
Q. What was the primary endpoint of 126 and 127?
A. The primary endpoint was relapse of -- having a relapse of either a manic episode or a depressed episode.

Page 1036

Q. Were trials 126 and 127 designed to determine if Seroquel can cause hyperglycemia?
A. No.
Q. Nevertheless, did AstraZeneca collect fasting glucose samples from the patients to monitor the glucose issues?
A. Yes.
Q. What were the efficacy results of trials 126 and 127?
A. Both 126 and 127 were robustly positive showing the decrease in relapse rates to both manic events and depressive events.
Q. Has AstraZeneca submitted the results of trials 126 and 127 to the FDA?
A. We submitted to the FDA and the indication was approved about two weeks ago.
Q. Prior to the submission of the results of 126 and 127 to the FDA, did there come a time when you analyzed

Page 1037

the glucose results from those studies?
A. Yes.
Q. Did you, in fact, do an extensive reanalysis of the results?
A. We did extensive additional analyses of the results of the glucose parameters.
Q. And why did you do that extensive reanalysis?
A. What we found in the pooled safety results was changes in blood glucose of similar magnitude that we had observed before. We also saw similar changes in hemoglobin A1c of the magnitude we had seen before. But in this trial, there were seven reports, seven adverse event reports of diabetes, six of which occurred in the Seroquel patients and only one occurred in the placebo patients. And that could have been a matter of chance, but we wanted to investigate whether or not there was a relationship between Seroquel and the emergence of diabetes. And we undertook

Page 1038

an extensive analysis of all of the data in that trial.
Q. Did that extensive reanalysis involve endocrinologists employed by AstraZeneca?
A. Yes.
Q. Did that reanalysis involve an endocrinologist who is not employed by AstraZeneca?
A. After extensive review and discussion internally, we presented the results to an external endocrinologist.
Q. And after an external discussion and after getting the results from the endocrinologist, was there a consensus among the SERM team about what the data revealed?
A. There was consensus among the clinical team that we took to SERM and we -- the data showed that there was an increase in the -- of about twofold in the rate of emergent hyperglycemia in patients who took Seroquel and a mood stabilizer compared to those that took a

EXHIBIT 12

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE:
SEROQUEL LITIGATION : MDL NO. 1769
:
THIS DOCUMENT RELATES:
TO ALL ACTIONS :

- - -

June 18, 2008

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of BARRY DAVID CHARLES ARNOLD, held at the Radisson Edwardian Manchester, Free Trade Hall, Peter Street, Manchester, England commencing at 9:14 a.m. before Linda L. Golkow, Registered Diplomate Reporter, Certified Shorthand Reporter.

- - -

Golkow Technologies, Inc.
877.370.3377 ph|917.591.5672 fax
deps@golkow.com

Page 362

Q. Is that a common symptom in people with diabetes?
A. It's actually a sign rather than a symptom, but it may be a sign of diabetes mellitus. But, of course, there are many other causes of ketonuria as well.
Q. Do you see where it says, "Seroquel discontinued about 3 months later. DM" or diabetes mellitus "reported to have resolved that same day." Do you see that?
A. Yes, I do.
Q. So, would that be an example of a positive dechallenge?
A. I would regard that as an example of a possible positive dechallenge. The data that's presented in front of me is not full. What we don't know is what concomitant medications the patient was on, we don't know whether those medications were stopped at the same time, and then, equally, what we don't know is, was the

Page 363

patient subject to some sort of dietary control at the same time as discontinuing Seroquel. So, this is a case that lacks complete data, and, therefore, it may appear as a positive dechallenge, but that has yet to be confirmed.
Q. Well, from the data that is presented, does this appear to be a case of positive dechallenge?
A. Well, the important thing is when you are --
MR. BROWN: Objection.
THE WITNESS: The important thing is when you're assessing individual clinical cases like this is that you assess them on the basis of a complete dataset if you're trying to categorize them in the manner that you seem to be attempting.
BY MR. BLIZZARD:
Q. Do you know what efforts were made by the company to get a complete dataset after analyzing this

Page 364

information here?
A. I do not know the specific details of the followup of this particular patient. I'm aware that the company has a standard operating procedure for followup. And to my experience, the data handling teams and the clinical teams who were managing adverse event reports follow that SOP very diligently.
Q. Would the fact that it resolved on the same day give you a clue that it might be a positive dechallenge?
MR. BROWN: Objection to the form.
BY MR. BLIZZARD:
Q. Would that be a pretty strong indication of a positive dechallenge, resolving on the same day that Seroquel was discontinued?
MR. BROWN: Objection.
THE WITNESS: The fact that it resolved on the same day may be taken as an indicator that it

Page 365

might be a positive dechallenge. I would not characterize it as being a clue, and I certainly wouldn't characterize it as being a strong indicator, as you suggest, due to the lack of data.
BY MR. BLIZZARD:
Q. If you look at the one that's second from the bottom of the first page, which is 2004UW06024, it's described as a nonserious event. Do you see this involved an 11-year-old male?
A. Yes.
Q. The dose was unknown, approximately six months, correct?
A. That's correct.
Q. And in the comments, does it say the preferred term was "blood glucose increased"?
A. So, that would be the reported event, yes.
Q. Then it said, "Patient" has arrow up or that would be increased "blood sugar," right?

Page 366

A. That is correct.
Q. And then "TX" -- that's treatment, isn't it?
A. That would stand for treatment.
Q. It says, "equals oral anti-diabetic med (unspecified). Seroquel discontinued. BS normalized," "BS" being blood sugar, correct?
A. That's correct.
Q. So, again, after Seroquel was discontinued, blood sugar normalized, correct?
A. It states that blood sugar was normalized. It implies that it was after Seroquel was discontinued. It doesn't state that factually, whereas the first patient that you indicated to me was very factual, reported to resolve that same day.
Q. Well, it says "Seroquel discontinued," and then the next sentence says "BS" or blood sugar "normalized," right?

Page 367

A. Yes. I'm just being very precise because you tried to use the word "then." That's an assumption or an implication.
Q. Okay.
So, when you're reading this, the blood sugar did not normalize after the Seroquel was discontinued?
A. No. I think it's an assumption that it normalized after discontinuation of Seroquel, but that's not -- should not be stated as a matter of fact, based upon the summary that's provided in this comments column.
Q. Well, we could look at the original adverse event report, couldn't we?
A. Yes, we could, and that perhaps might be more informative.
Q. And do you really think that it was normalized before Seroquel was discontinued?
A. I'm just dealing with facts for the purpose of this jury. I think

Page 368

that you've made an assumption that it's normalized afterwards. I'm not saying that that's not a reasonable assumption. I'm just saying it's an assumption, rather than a statement of fact.
Q. Well, let's go to the next one then. See, this is 2004UW08948. This is a 7-year-old male, correct?
A. It appears that way, yes.
Q. This is a 7-year-old male taking 300 milligrams daily, correct?
A. Yes.
Q. It says the PTs is "Hypoglycemia, Hyperglycemia, Lipids increased," right?
A. That's correct.
Q. It then says, "Patient had decreased blood sugars and increased blood sugars"?
A. Yes.
Q. "BS fluctuating from 42 (fasting) to 202 (1 hour after fruit), HbA1c equals 4.9%, GTT equals 99 (2 hours post glucose). Patient also had

Page 369

increased lipids (no lab data). Seroquel discontinued within one week positive blood sugars back to normal."
Do you see that?
A. Yes.
Q. Is that a case of a positive dechallenge?
A. It's an apparent case of positive dechallenge, but I'm not sure what it's a positive dechallenge to, because it says blood sugar back to normal, but we don't know whether that's referring to the decreased blood sugar, hypoglycemia, or the increased blood sugar, hyperglycemia.
I'd also remark that the HbA1c of 4.9 percent, to my knowledge, that does not equate with a HbA1c level that matches hyperglycemia. Patients who are hyperglycemic who may be tending towards diabetes, you would expect a higher HbA1c than that. So, yes, it appears to be a positive dechallenge, but I'm not sure what event is actually being

EXHIBIT 13

INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT

Tel No: 01625 517679

To: See Below

From: Richard Lawrence

Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

Richard

Distribution:

To:	Don Stribling	(STRIBLING D@A1@APVXC1)
CC:	Lisa A. Arvanitis	(ARVANITIS LA@A1@UWP00)
CC:	Don Stribling	(STRIBLING D @ A1 @ APVXC1)
CC:	Richard Lawrence	(LAWRENCE RA @ A1 @ APVXC1)
CC:	Athena M. Ruhl	(RUHL AM@A1@UWP00)
CC:	Chris R. Griffett	(GRIFFETT CR@A1@UWP00)
CC:	Ricky Bache	(BACHE RA @ A1 @ APVXC1)
CC:	Joher Raniwalla	(RANIWALLA J1 @ A1 @ APVXC1)
CC:	Georgia L. Tugend	(TUGEND GL@A1@UWP00)

EXHIBIT 14

From: Tumas John JA
Sent: 5/11/1999 1:20:48 PM
To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J; Tumas John JA
CC: Goldstein Jeffrey JM
Subject: RE: Small Review

Dear All,

Thank you to those who have commented on this review - I will collate the comments
and pass them on to Dr. Small.Â Dr. Small has contacted Jeff and explained
that the schedule for this review has been moved up.Â We will now have to send
our comments to her tomorrow (Wednesday).Â Therefore, if anyone has any further
comments, please pass them along.

Best regards,

John

From: Â Tumas John JA
Sent: Â Wednesday, May 05, 1999 9:47 AM
To: Â Â Â Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price
Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor
IW; Raniwalla Joher J

Cc: Â Â Â Goldstein Jeffrey JM
Subject: Â Â Â Â Â Â Small Review
Importance: Â Â Â High

Dear All,

Attached is a draft review of quetiapine by Dr. Joyce Small.Â You may recall,
Dr. Small was the lead investigator for Trial 8, high dose, low dose quetiapine
vs placebo.

Dr. Small has asked that we review the document to ensure that the most current
information is included.Â May I ask that comments be limited to this request
and any inaccuracies found.Â She is not looking for editing support and would
like to keep Zeneca's influence on this review minimal.

Please return any comments to me by Thursday, May 13.

Best regards,

John

<<File: QUETIAPI.NE.doc>>

From: Hough Nick NW
Sent: 5/10/1999 9:06:26 AM
To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J; Tumas John JA
CC: Goldstein Jeffrey JM
BCC:
Subject: RE: Small Review

John,

here are my comments on 'Small', some of which reflect my usual concerns, ie selective use of QUEST, overlooking what happened in study 14 etc; however there are also some obvious positive messages that could be added:

* elderly data should be based on 52 weeks if possible
* selective inclusion of QUEST data and not COSTAR means that this paper is unsuitable for 'promotional purposes' - this paper goes even further than the visual aid ('data display' approach?) since the author actually makes a comparative statement - 'with advantages for QTP on depression ratings and the CGI'
* therefore, not 'approvable' for international promotional purposes
* selective inclusion of QUEST data is in conflict with our publication policy since we have no plans to do anything with COSTAR
* study 14, the head to head comparison against haloperidol unfortunately resulted in a 'p-value' in favour of HAL on the positive sympton scale; therefore it is not possible to say that relief of positive symptoms appears comparable to standard neuroleptics
* 1st para under 'neurological effects' tends to switch back and forth between the HAL and CPZ comparative data and doesn't flow logically therefore
* could perhaps include the CLOZ to QTP switch data wrt to weight gain 'reversal'/ improved diabetic symptoms ??
* need medical check on what is said wrt ECG/ QTc intervals
* under therapeutic potential, 2nd para - 'studies of these applications' ...this is written as though something has been described immediately previously relevant to this statement??

Hope this is helpful,

Cheers,

Nick

>----------
>From: Tumas John JA
>Sent: 05 May 1999 14:47
>To: Murray Michael MF; Davies Diane DE - MMCC; Lawrence Richard RA; Price Anna AC; Hough Nick NW; Jones Martin AM - PHMS; Litherland Steve S; Rak Ihor IW; Raniwalla Joher J
>Cc: Goldstein Jeffrey JM
>Subject: Small Review
>Importance: High
>
>Dear All,
>
>Attached is a draft review of quetiapine by Dr. Joyce Small. You may recall, Dr. Small was the lead investigator for Trial 8, high dose, low dose quetiapine vs placebo.

>
>Dr. Small has asked that we review the document to ensure that the most current information is included. May I ask that comments be limited to this request and any inaccuracies found. She is not looking for editing support and would li>ke to keep Zeneca's influence on this review minimal.
>
>Please return any comments to me by Thursday, May 13.
>
>Best regards,
>
>John
>
><<File: QUETIAPI.NE.doc>>
>

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

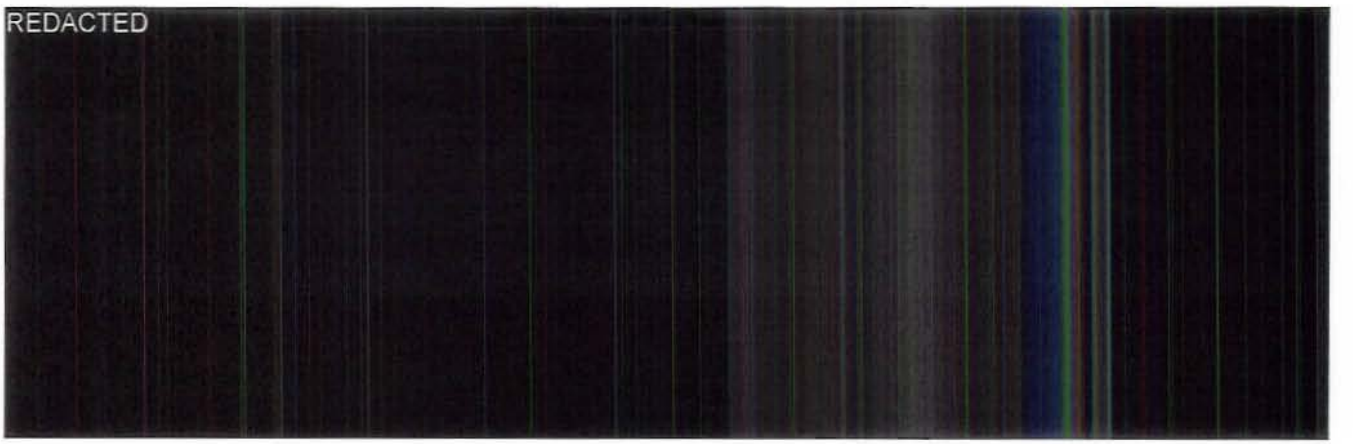
FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL



Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>
Judith Owens
Ext: 24164
11F34 Mereside

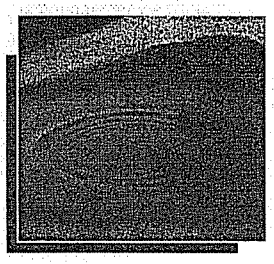
EXHIBIT 15

Managing Weight Gain and Diabetes in Schizophrenia

A Patient Case Study

From the files of
Michael J. Reinstein, MD

Forest Foundation, Inc.
Clinical Research Department
Community Mental Health
Chicago, Illinois



Patient Presentation

- A 49-year-old white male, unemployed, with a long history of psychiatric hospitalizations dating from age 25
- His various diagnoses include acute schizophrenic episode, paranoid schizophrenia, bipolar disorder, and schizoaffective disorder
- The patient also has a history of alcohol abuse

Past Medical/ Psychiatric History

- The patient was first hospitalized in 1976 with religious delusions, auditory hallucinations, and withdrawal
- He was subsequently hospitalized on several different occasions and followed on an outpatient basis after each discharge

Personal History

- There is no family history of psychiatric illness
- The patient was married with a son but has not had contact with either his wife or son for over 20 years
- He has not been gainfully employed for over 15 years
- He lives sporadically with either his mother or in homeless shelters

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia. If its signs and symptoms appear, discontinuation should be considered.

Mental/Physical Evaluation

- At presentation, the patient was alert and oriented to time, place, and person, maintained good eye contact, and was stable and in a cooperative mood
- Intelligence appeared to be within normal range
- He denied any hallucinations or ideas of reference
- No EPS, rigidity, or ataxia; no suicidal or homicidal ideations were expressed
- Judgment and reality contact were impaired, he appeared to have no insight, and he frequently laughed inappropriately in response to internal stimuli
- The patient answered questions only after considerable pauses—very briefly and in a low tone and volunteered no information whatsoever
- Physical evaluation revealed a patient overweight by approximately 10 lb

Treatment with SEROQUEL, like other antipsychotics, may result in somnolence, especially during initial dose titration.

Rationale for SEROQUEL Therapy

- Previous treatment with olanzapine 10 mg/day resulted in significant weight gain (10 lb) and subsequent development of type II diabetes (NIDDM)
- Accu-Chek™ was scheduled tid with sliding scale of Humulin® insulin

"This patient demonstrated some classic negative symptoms—blunted affect, emotional withdrawal, poor rapport, lack of spontaneity. Negative symptoms can often be very difficult to treat. We chose SEROQUEL for this patient because in our experience it provides excellent results with negative psychotic symptoms, and weight gain with SEROQUEL hasn't been an issue."

—Michael J. Reinstein, MD

Seroquel®
quetiapine fumarate 25 mg, 100 mg & 200 mg tablets

For a more normal life

Please see accompanying full prescribing information.

SEROQUEL Dosing Regimen

- Olanzapine therapy was discontinued due to weight gain and the development of diabetes
- SEROQUEL was initiated at 150 mg/day for 1 week
- The SEROQUEL dose was then increased to 300 mg/day where it remains

Response to SEROQUEL

- The patient has shown a positive response to SEROQUEL, becoming more spontaneous, more interested in his surroundings, and has demonstrated improved interactions with others
- Blood glucose levels were brought under control, permitting the substitution of an oral hypoglycemic agent for insulin treatments
- Metabolic stability was maintained, allowing the patient to discontinue the hypoglycemic agent and return to a normal diet
- Not only did the patient not gain weight with SEROQUEL, he lost approximately 8 of the 10 lb gained while on olanzapine

"Our laboratory data revealed a normalization of serum glucose levels which is valid proof of improvement of diabetes and metabolic stabilization. His psychotic symptoms were well controlled, including the negative symptoms. The patient lost weight (8 lb) and is very pleased about this. He is also relieved that he no longer has to take daily insulin injections."

—Michael J. Reinstein, MD

Follow Up

- After 7 months, the patient remains well on SEROQUEL 300 mg/day
- The patient is currently taking part in a research study, where he perceives himself as a partner in a joint endeavor. He has achieved clinical improvement and a better quality of life
- He denies having any side effects and is considered competent to handle his own funds and supervised self-medication

"We have found SEROQUEL to be ideal in patients who have problems with weight gain and, due to this, the development of diabetes. In this patient, once olanzapine was discontinued and SEROQUEL was started, the weight was lost, the diabetes resolved, and the patient was able to stop taking hypoglycemic medication. In our experience, weight gain is not an issue with SEROQUEL, unlike some other antipsychotic medications."

—Michael J. Reinstein, MD

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported, and prescribing should be consistent with the need to minimize the risk.

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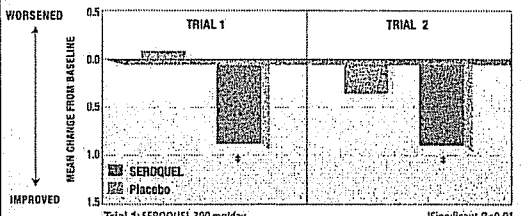
The Strength to Control Both Positive and Negative Symptoms

Across well-controlled trials

Consistent Efficacy in the Treatment of Positive Symptoms[1-4†]

Mean Change in BPRS* Positive Symptom Cluster Scores (LOCF)[1-4†]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)
†Significant $P<0.01$

- **SEROQUEL significantly reduced positive symptom scores**

SEROQUEL was compared with placebo in the following well-controlled, 6-week, acute-phase, multicenter trials.

Trial 1: fixed doses of 75, 150, 300, 600, and 750 mg/day of SEROQUEL (n=255), placebo (n=51).

Trial 2: titrated doses up to 250 mg/day (low dose, n=94) and up to 750 mg/day (high dose, n=96) of SEROQUEL, placebo (n=96).

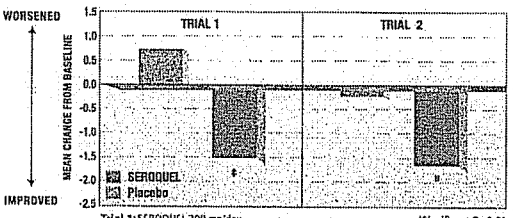
*BPRS: Brief Psychiatric Rating Scale is a clinical assessment tool that measures a combination of 18 individual positive, negative, and general symptom items. The BPRS positive symptom cluster score is the mean of 4 of the 18 individual symptom items for the clinical assessment of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

†LOCF: Last Observation Carried Forward.

Precautions listed in the label include orthostatic hypotension and the risk of cataract development.

...and Consistent Efficacy in the Treatment of Negative Symptoms[1-4†]

Mean Change in SANS‡ Summary Scores (LOCF)[1-4]



Trial 1: SEROQUEL 300 mg/day
Trial 2: SEROQUEL 500 mg/day (mean dose, high-dose group)
†Significant $P<0.01$
*Significant $P=0.02$

- **SEROQUEL significantly reduced negative symptom scores**

‡SANS: Modified Scale for the Assessment of Negative Symptoms is used to assess the negative symptoms associated with schizophrenia. The SANS summary score is a total of 5 global items: affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality, and attention.

The most common adverse events leading to treatment withdrawal were somnolence (0.8%) and hypotension (0.4%).

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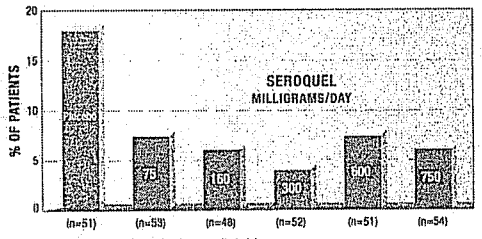
AZSER10427477

Outstanding Overall Tolerability Across the Entire Dose Range

Across the entire dose range,* an EPS† profile no different from placebo

EPS Adverse Events by Dose[1‡]

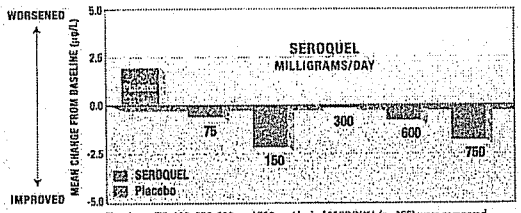


*In a 6-week, acute-phase, placebo-controlled trial.
†EPS: Extrapyramidal Symptoms were defined as dystonia, akathisia, and parkinsonism.
‡Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- No dose-related EPS were associated with treatment with SEROQUEL® (quetiapine fumarate)[5]

Across the entire dose range, plasma prolactin levels no different from placebo[1]

Mean Change in Plasma Prolactin Levels[1]



Five doses (75, 150, 300, 600, and 750 mg/day) of SEROQUEL (n=255) were compared with placebo (n=51) in a 6-week, well-controlled, acute-phase, multicenter trial.

- There were no statistically significant differences in plasma prolactin levels between any group taking SEROQUEL and the placebo group[1]

Minimal Weight Gain

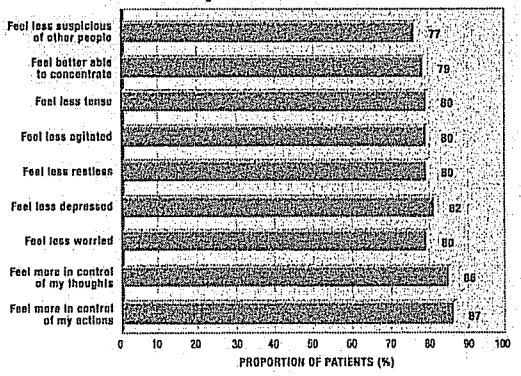
- In a recent open-label study, only 2.5% of patients treated with SEROQUEL (n=553) reported weight gain[6]

Patient Preferred

In a survey of patients (n=129) using SEROQUEL[7]

- 97% reported that they preferred SEROQUEL to previous medications
  - —Two reasons for preferring SEROQUEL were efficacy (29%) and tolerability (41%)[7]
- Benefits noticed in the last 6 months by patients using SEROQUEL

Efficacy-Related Benefits[7]



As with other antipsychotic agents, SEROQUEL has been associated with weight gain. However, in all placebo-controlled clinical trials, weight gain was approximately 5 lb, which occurred mainly during the early weeks of treatment.[5]

Please see accompanying full prescribing information.

EXHIBIT 16

Clin Drug Invest 1999 Aug; 18 (2): 99-104
1173-2563/99/0008-0099/$03.00/0

Effect of Clozapine-Quetiapine Combination Therapy on Weight and Glycaemic Control

Preliminary Findings

Michael J. Reinstein, Larissa A. Sirotovskaya, Lynne E. Jones, Sangarapillai Mohan and *Maxim A. Chasanov*

Clinical Research Department, Forest Foundation Inc., Chicago, Illinois, USA

Abstract

Objective: The purpose of this open-label, non-randomised, 10-month, retrospective comparative study was to assess changes in weight and diabetes status for patients initially treated with clozapine who developed diabetes and who were then switched to clozapine-quetiapine combination therapy.

Methods: Sixty-five clinic charts were reviewed. All patients were from long-term care facilities. Bodyweight data were collected for this group of 65 randomly selected schizophrenic patients who were on clozapine initially (200 to 800 mg/day for 6 months) and then had quetiapine ('Seroquel') added to their therapy. Clozapine dosages were reduced as quetiapine was added proportionally: 25% of the clozapine dose was changed to quetiapine, using a ratio of exactly 1mg clozapine to 2mg of quetiapine. The quetiapine dosages ranged from 200 to 800 mg/day. This means that each patient received 6 months of clozapine therapy followed by 10 months of combination treatment with clozapine-quetiapine. Weights were recorded monthly, and diabetes status was also performed for patients who developed the condition during clozapine monotherapy.

Results: Changes in weight and the status of diabetes were determined in patients switched from a 6-month clozapine therapy to the 10-month combination clozapine-quetiapine treatment. All changes were statistically significant ($p < 0.001$). Use of this combination therapy in the management of weight gain and diabetes resulted in a 100% satisfactory response. All 65 patients showed weight loss ranging from 0.22 to 10.5kg (0.5 to 23lb) [mean 1.8kg (3.98lb)] after the first month of combination therapy, and the improvement continued through the study duration (10 months). Marked total weight loss ranged from 0.45 to 18.6kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period. 20% of patients (13 patients) who developed diabetes during the 6-month clozapine monotherapy showed significant improvement of disease status with addition of quetiapine. Compliance with medication was 100% and no significant adverse events were observed. The most common adverse event reported by patients was drowsiness. However, this did not contribute a valid reason for discontinuation of clozapine-quetiapine therapy and could be

corrected by dosage adjustment at any time of the report of this adverse effect by patients.

Conclusion: An unexpected, yet welcome, clinical effect of quetiapine is its apparent propensity to induce weight loss and improve glycaemic control in patients who gain weight and develop diabetes on clozapine therapy. The results of this retrospective study support the safety and tolerability of clozapine-quetiapine combination therapy.

Antipsychotic drugs can cause pronounced weight gain. This phenomenon can be regarded as a pharmacologically-induced adverse event and every effort must be made to prevent or vigorously treat it.[1] Clozapine is an atypical antipsychotic agent considered to have superior efficacy for patients with treatment-resistant psychosis.[2] No other atypical antipsychotic agent has been reported to be as effective as clozapine to date. Nonetheless, long-term administration of clozapine markedly influences eating behaviour and increases bodyweight in humans.

It is well known that weight gain is a serious undesirable effect of clozapine therapy, but the mechanism of clozapine-associated weight gain remains uncertain. Discussing neuroleptic-associated weight gain, Brady[9] noted that the mechanism is likely to be multifactorial. Possibilities include drug effects on serotonergic, anticholinergic and histaminic neurotransmitter systems, in addition to effects on endocrine and metabolic functions.

The complication of weight gain can result in noncompliance and a consequent return of psychotic symptoms.[3] Such an outcome can assume major clinical importance in the management of chronic schizophrenia, where maintenance of psychological and social well-being is dependent on regular administration of antipsychotic drugs.

Moreover, many patients with schizophrenia suffer from obesity,[4-6] which is associated with excessive rates of morbidity and mortality;[7] obesity is well recognised to be associated with an increased risk of morbidity from such conditions as diabetes, cardiovascular disease and locomotor disorders.[8] Particularly in these patients, additional weight gain is to be avoided.

Quetiapine ('Seroquel') is one of the most novel antipsychotic agents developed with the benefit of recent research. Quetiapine is an atypical drug for the treatment of schizophrenia or a related psychotic or schizoaffective disorders. Based on preclinical and recent clinical studies, quetiapine appears to have a pharmacological profile similar to that of clozapine without many of the latter drug's serious adverse effects, including weight gain and the development of diabetes.

The current retrospective study was undertaken to determine whether coadministration of clozapine and quetiapine could prevent the significant adverse effects of weight gain and development of diabetes experienced by schizophrenic patients taking clozapine only.

Patients and Methods

Study Participants

The target population consisted of all schizophrenic patients who were resident in Chicago's long-term care facilities. They were men and women ≥18 years of age who met DSM-IV criteria for schizophrenia and schizoaffective disorder. Those who demonstrated weight gain and/or developed diabetes during 6 months' treatment with clozapine monotherapy were eligible for the study.

Patients were receiving clozapine monotherapy and switched to clozapine-quetiapine. We evaluated changes in weight during clozapine monotherapy and clozapine-quetiapine combination therapy and status of diabetes in those developing it during the clozapine treatment time.

The study protocol and consent forms were

approved by the local institutional review board. Written informed consent was obtained from each participant before the start of the study.

Methods

We employed an open-label, non-randomised design using retrospective chart review to identify patients and obtain data. Bodyweight data were collected for a group of 65 randomly selected schizophrenic patients who gained weight, and 13 (20%) of whom developed diabetes, while being treated with clozapine for 6 months and who were then switched to combination clozapine-quetiapine therapy. Clozapine dosages were 200 to 800mg per day. Clozapine was tapered up to 25% of the current dose and quetiapine was added proportionally: 1mg clozapine was substituted for 2mg of quetiapine. The quetiapine daily dosages ranged from 200 to 800mg.

Weight was recorded at baseline, monthly and at the conclusion of the study. Each patient was weighed monthly during the last 10 months of combination clozapine-quetiapine therapy and patients' diabetes status was determined concurrently by recording monthly blood glucose levels.

During the period of clozapine monotherapy, results of routine chemistry examinations revealed marked hyperglycaemia for the 13 patients (20%) who developed diabetes. Serum glucose levels were noted to be 0.36 to 0.85 mg/L, with a mean of 0.675 mg/L. Long-term control of hyperglycaemia was assessed by measuring glycosylated haemoglobin (HBA_{1c}) in fasting patients. Levels of HBA_{1c} were significantly higher than normal for patients who developed diabetes during clozapine monotherapy.

The onset of a response to clozapine-quetiapine combination therapy was defined as the initial appearance of clinical improvement with regard to significant weight loss and noticeable improvement of diabetes status.

Each of the 13 patients with diabetes began a regimen of regular insulin and a diabetic diet. Three patients discontinued hypoglycaemic agents and were placed on a regular diet. During the first 5 to 6 months of combination clozapine-quetiapine therapy, insulin requirements decreased and insulin was later discontinued. A regimen of the oral hypoglycaemic drug glibenclamide (glyburide) at 3 to 4 mg/day was started. Patients who showed a rapid resolution of all symptoms were placed on a regular diet.

Our primary goal was to show significant weight loss during the combination therapy. The second aim was to show that diabetes status could be improved during the combined clozapine-quetiapine therapy.

Statistical Analyses

Statistical analyses were performed on data from the intent-to-treat population, which comprised all 65 patients given the study medication. The statistical significance of improvement from baseline in both weight gain ($p < 0.001$) and effect on blood glucose levels ($p < 0.0001$) was calculated by paired t-tests. Patients were monitored monthly for a response to treatment and adverse effects. Data from all those who reported adverse events as well as improvement in the primary targeted symptom (weight loss and improvement of diabetes during this time) were tabulated in medical records.

Results

All 65 patients (100%) who commenced taking combination clozapine-quetiapine therapy showed significant weight loss and improvement in diabetes status during the period of combined clozapine-quetiapine therapy.

Weight Loss

At baseline, weight ranged from 59.5 to 125kg (131 to 275lb) [mean 104kg (229.2lb)]. During clozapine monotherapy, across all patients, the mean weight gain was 6.5kg (14.3lb; 6.25%) for the period of 6 months.

Marked changes in bodyweight were observed when patients started treatment with clozapine-quetiapine combination therapy. The quetiapine

dose at 1 month ranged from 200 to 800mg per day. The individual weight loss ranged from a minimum of 0.23kg (0.5lb) after the first month of treatment to a maximum of 18.6kg (41lb) at the conclusion of the study [mean 9.4kg (20.75lb)].

All the changes in bodyweight were statistically significant ($p < 0.001$). All 65 patients showed weight loss ranging from 0.23 to 10.5kg (0.5 to 23lb), with a mean loss of 1.8kg (3.98lb), after the first month of combination therapy. Subsequent monthly losses were 1.8kg (3.98lb), 1.796kg (3.96lb), 1.456kg (3.21lb), 1.12kg (2.47lb), 0.966kg (2.13lb), 0.68kg (1.50lb) 0.635kg (1.40lb), 0.408kg (0.90lb), 0.318kg (0.70lb) and 0.227kg (0.50lb).

The improvement continued throughout the study to the end-point (10 months). Marked total weight loss ranged from 0.45 to 18.61kg (1 to 41lb), with a mean loss of 4.2kg (9.2lb) over the 10-month study period.

Diabetic Status

Twenty percent of the 13 patients who developed diabetes during clozapine monotherapy showed significant clinical and laboratory improvement of diabetes while taking clozapine-quetiapine. Weight gain in this group of patients ranged from 3.2 to 24.1kg (7 to 53lb) [mean 8.5kg (18.69lb)] during clozapine therapy. Thirteen patients who developed diabetes due to clozapine showed significant weight loss, with a mean loss of 1.75kg (3.84lb) after the first month of combination treatment and 4.68kg (10.3lb) at the conclusion of the study.

During clozapine therapy, patients showed significant increases of up to 10 to 15% in the HBA_{1c} level (monthly mean increase = 1.34%). HBA_{1c} levels returned to normal (<7%) at the end of the study (monthly mean decrease = 0.78%): results of routine chemistry examinations at the end of the 10-month treatment period revealed normalisation of blood glucose levels, resulting in a rapid decrease in insulin requirements and/or discontinuation of insulin treatment and starting of a regimen of an oral hypoglycaemic agent. Three patients who discontinued hypoglycaemic agents were placed on a regular diet and remained metabolically stable.

Positive results were assessed in terms of normalisation of blood glucose levels, discontinuation of insulin therapy, switch of patients to oral hypoglycaemic drug and placement of patients on a regular diet. According to our data, results of a laboratory examination revealed a normalisation of serum glucose levels in three of our patients, which is valid proof of improvement of diabetes and metabolic stabilisation.

Overall, our data demonstrated that no adverse behavioural changes occurred during the 10-month study period. No patients stopped therapy because of drowsiness; this was corrected by adjusting the dose. Compliance with medication was 100% and no significant adverse events were observed.

Discussion

The multiple clinical studies and reports from different researchers demonstrate significant weight gain in a group of schizophrenic patients during clozapine treatment. In spite of the considerable efficacy of clozapine, increased appetite, craving for sweets and weight gain are commonly cited by patients as their primary reason for discontinuation of the treatment.

The mechanism of clozapine-associated weight gain remains uncertain, as does the cause of hyperglycaemia associated with high doses of clozapine.

The first report of severe insulin-dependent hyperglycaemia precipitated by clozapine therapy in a patient with a previously unremarkable medical history was introduced by Kamran et al. in 1994.[10] According to his report, the sustained hyperglycaemia, which required insulin therapy and diet modification, completely resolved following discontinuation of clozapine, but he continued 'we do not know whether clozapine alone or the combination of clozapine, benztropine, and ranitidine was responsible for the hyperglycaemia'.[10]

The majority of patients in our current study were on valproate semisodium (divalproex sodium). Thus, the possibility that drug combinations

may have affected the metabolism of one or more agents, resulting in altered drug levels and impaired glucose metabolism, must be kept in mind.

Diabetic ketoacidosis associated with clozapine treatment was also reported by Koval et al.[11] The author described a history of diabetes for a patient who did not have elevated serum glucose levels previously. This patient developed diabetes 6 months after initiation of clozapine treatment and was admitted to an intensive care unit in a comatose condition. She initially required insulin treatment. Clozapine treatment was discontinued slowly, and her insulin requirements decreased and insulin was later discontinued. This case also demonstrates that clozapine may precipitate insulin-dependent diabetes in some individuals. Further studies are necessary to investigate the relationship between clozapine therapy and blood glucose regulation.

Quetiapine is a recently introduced antipsychotic drug. In its pharmacological profile, quetiapine resembles other atypical antipsychotic agents with the exception of possible weight gain. An unusual clinical effect of the drug is its apparent propensity to induce weight loss, which could be a cause of the improvement of diabetes during combination clozapine-quetiapine therapy. There are obvious clinical implications arising from the propensity of an effective antipsychotic drug to produce weight loss as well as cause improvement in, and in some cases resolve, diabetes, leading to discontinuation of insulin or other hypoglycaemic drugs.

A great deal of work remains to be done with quetiapine, in particular to elucidate its mechanism of action and to determine the optimal dosage and length of treatment in combination with clozapine.

The current retrospective analysis was done to determine whether coadministration of clozapine and quetiapine could attenuate the significant unpredictable adverse effects of weight gain and development of diabetes during clozapine monotherapy.

This study may contribute to the discovery of novel therapeutic approaches to the treatment of refractory schizophrenic patients with clozapine and quetiapine without serious adverse effects such as significant weight gain and development of diabetes, which can occur during clozapine monotherapy.

To date, no study had compared clozapine monotherapy and combination clozapine-quetiapine therapy. Future studies should focus on larger sample sizes to corroborate the findings of the current study. Furthermore, a double-blind, randomised, prospective study would have been preferable. Limitations of this current retrospective analysis are non-standardised administration, uncontrolled concomitant therapy, non-randomised assignment and data censoring.

Conclusion

The current study demonstrated that the combination of clozapine and quetiapine had a significant, positive effect on weight and glycaemic control.

Acknowledgements

This study was supported by a grant from Zeneca Pharmaceuticals Inc., Delaware, USA. 'Seroquel' is a trademark, the property of Zeneca Pharmaceuticals Limited.

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11. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. Am J Psychiatry 1994; 151: 10

Correspondence and reprints: Dr *Michael J. Reinstein*, Forest Foundation Inc. Clinical Research Department, 4755 North Kenmore Ave., Chicago, IL 60640, USA.

EXHIBIT 17

From: Beamish, Don G
Sent: Monday, November 05, 2001 10:24 PM
To: Pusey, James M
Cc: Tugend, Georgia L
Subject: FW: Reinstein Response Letter and Backgrounder

Importance: High

Attachments: Reinstein Response.doc; Reinstein Backgrounder.doc
James,

Georgia has spoken to Dr. Reinstein directly and has drafted the attached response to his letter. Georgia has also provided some background information that would not be sent to Dr. Reinstein. I would recommend that the letter should be sent from Georgia. I think it is important for Georgia to maintain her relationship with Dr. Reinstein and be viewed as his key contact. As I suggested in my previous memo, I also think it would be appropriate for me or someone else in a leadership role to acknowledge his concerns directly either in a phone call or in a follow up letter. Please let me know how you would like to proceed.

Don

-----Original Message-----
From: Tugend, Georgia L
Sent: Monday, November 05, 2001 4:49 PM
To: Beamish, Don G
Subject: Reinstein Response Letter and Backgrounder
Importance: High

November 5, 2001

Michael J. Reinstein MD, PC
Community Mental Health Services
4755 North Kenmore
Chicago, IL 60640

Dear Dr. Reinstein,

I am in receipt of your in your letter dated October 23, 2001 to David Brennan. and hope to address the points you raise.

Here at AstraZeneca we are aware of the critical nature of our relationship with you and your colleagues that has been established with individuals from our Sales, Marketing, and Medical functions. We value the contribution that you, as an important customer, have made toward the success of SEROQUEL and appreciate your candid feedback to us.

Regarding your first point, there is little doubt that Janssen has funded more research in support of risperidone in the past than AstraZeneca did for SEROQUEL. This, while not ideal for us, is not surprising given that risperidone was launched nearly 4 years before SEROQUEL and that Janssen does provide significant resources to the #1 drug in their overall business. This has resulted in a rich research portfolio to date. However, like you, we recognize the excellent attributes and benefits of SEROQUEL and with its current level of success and its promise for even greater market penetration, the company has increased resources in support of its clinical development program and commercial activities so that past trends may well reverse

There really is no dispute regarding the second point you raise regarding communication of dosing issues. One of the greatest challenges SEROQUEL has faced is ensuring that the appropriate dose in used. The dosing strategy was never to limit use to 300 mg/day but because of trials submitted to the FDA for registration, the Prescribing Information contains the statements "initial target dose of 300-450 mg/day" and dose limit of 800 mg/day for safety. This led to confusion and uncertainty in the minds of some prescribers, which we have aggressively attempted to address in numerous promotional and educational programs over the past several years.

Thank you for bringing the reimbursement issue to our attention. We have confirmed that Omnicare in Chicago is denying claims beyond 800 mg/day of SEROQUEL. They apparently are doing likewise with another atypical antipsychotic. While we will work with our Account Directors and Advocacy Groups to alleviate this situation in the near term, your point to do research to obtain a higher dosing ceiling is well taken.

AstraZeneca prides itself at being a customer-focused organization and as such timely payments of honoraria and reimbursement for expenses is essential. We have put a new system in place for the payment of honoraria but we realize there is room for improvement particularly around travel and other out-of-pocked reimbursements. Likewise an AstraZeneca speaker should not be inconvenienced if a program is cancelled for reasons outside their control and we will address this with our Professional Relations and Sales Departments.

We value the contributions of leaders in Psychiatry such as yourself and appreciate our long-standing relationship with your group. And although we must balance the needs of AstraZeneca products across the entire business portfolio, please let me assure you that the company is in complete support of SEROQUEL and hope to have your continued support as well.

Sincerely,

Background: letter from M. Reinstein, et al to D. Brennan, dated Oct. 23, 2001

This group does generate a very significant amount of SEROQUEL sales for us. They run several clinics in the city of Chicago and by all accounts have over 1,000 patients on SEROQUEL. While likely not "the largest prescribers of SEROQUEL in the world", they probably are in the top 5 in the US.

Because of their patient volume they are attempting to establish themselves as a research center.

This group, in particular John Sonneberg PhD, Director of Research has been extremely persistent in recent months with demanding research from AZ. Their comments to several AZ employees suggest since they use large volumes of SEROQUEL they should by default be doing research on our behalf. They have further implied that should they not get research funding that they would switch patients currently on SEROQUEL to competitive agent(s).

Our Clinical colleagues have significant and numerous issues in past with the quality of research that this group has produced in the past. Matters such as not getting informed consent from study participants, modification of protocols without permission, etc has made the business understandably reluctant to place studies with this group. There is little confidence that Good Clinical Practices can be adhered to. Their research is often criticized by peers in Psychiatry.

However, in attempts to have a "win-win" for all, we have offered funding for projects such as retrospective chart reviews (as opposed to well-controlled, double blinded trials) that could do little harm but still demonstrate commitment to the customer. The group has not accepted this and they continue to insist on funding to do a high dose SEROQUEL trial (>1600 mg/day) that is addressed in Point 2 of their letter.

Drs. Reinstein and Chasnov are prolific speakers on our behalf and are particularly influential with prescribers outside the Chicago regional area. They get numerous speaking engagements because of their own experience and belief in the brand. (Note: they are generally held in poor regard among their peers in the greater Chicago area).

Because of their importance to our business, they have had an extraordinary amount of attention given to them. A number of AZ personnel from numerous functions have had open, honest but collegial, cordial dialog with Drs. Reinstein and Sonneberg. Contact has been with Sales, Marketing, USDD, and Scientific Commercialization at several levels, including Leadership levels within our organization. All involved have had extremely good communication internally and with the customers to address their interests. Every discussion appeared to be well received at that time. However, actions like this letter and other persistent calls demanding research continue to occur despite our attention to their group, thus disappointment with the "time for new leadership" remark.

EXHIBIT 18

DISCUSSION DOCUMENT

SEROQUEL™

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

SERM NO 32 - 22 JUNE 2000 - MINUTES

Participants : M Brecher

After review of the available data SERM considered that no amendment to the CDS was justified

ACTION - WG create a position paper.
MB keep this under review and bring back to SERM the expected additional clinical trial data

AUTHOR(S):

Wayne K. Geller MD
Medical Director, Drug Safety
Wilmington, DE

SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

Presently, the SEROQUEL Core Data Sheet (CDS) does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with SEROQUEL therapy. Safety data derived from clinical trials and spontaneous reports, despite often containing limited information, suggest the possibility of an association between SEROQUEL use and impaired glucose regulation including occasional reports of new onset diabetes mellitus. While none of these reports are absolutely steadfast, the number of reports is fairly sizeable. Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis. While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for SEROQUEL and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for SEROQUEL for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The SEROQUEL core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with SEROQUEL:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The SEROQUEL US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels $\geq$110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

(1) Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or

(2) Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or

(3) Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with
Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:

Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)

- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12 to 16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

(1) The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).

(2) Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases.

Case Number: 2000UW01164

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started SEROQUEL 200 mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on SEROQUEL. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving SEROQUEL, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving SEROQUEL 300 mg daily since 06 December 1999. On 26 January 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. SEROQUEL was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include zoloft, klonopin, haldol and depakote.

Follow-up 23 February 2000: Pharm D reports that "after further testing, the attending physicians did not feel that SEROQUEL was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving SEROQUEL and developed diabetes. Physician feels that SEROQUEL may possibly be responsible for the development of diabetes.

Follow-up 11 November 1999: Physician reports that the 47 year old female (not 45) had been receiving SEROQUEL 600 mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. SEROQUEL was tapered for discontinuation. Concomitant medications include klonopin and benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "SEROQUEL caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS

A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving SEROQUEL 100 mg every evening since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of SEROQUEL was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 September 1999, SEROQUEL dosage was again decreased to 25 mg every evening. The patient had been receiving risperidol prior to

SEROQUEL. Concomitant medications include ritalin for attention disorder and serzone for depression.

Case Number: 1999UW00969

COMPLICATIONS OF DIABETES MELLITUS

A report has been received from a physician concerning a 28 year old male patient who was taking SEROQUEL and lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14 March 1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.

*Follow-up received 22 March 1999: A pharmacist reports that the patient started zithromax on 10 March 1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14 March 1999: The patient presented on 14 March 1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15 March 1999. The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05 May 1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10 to 16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967

DIABETES

A report has been received from a physician concerning a 17 year old male who is receiving SEROQUEL 200 mg twice daily for schizophrenia. The patient was initially started on 100 mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300 mg daily. Patient also receives paxil and depakote. Patient continues on SEROQUEL.

Case Number: 1999UW00288

BLOOD SUGAR RISING

A report has been received from a 58-year-old diabetic female patient who has been receiving SEROQUEL since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 January 1999 the reading was 321.

Case Number: 1999AP06660

LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA

A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving SEROQUEL since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300 to 400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started SEROQUEL in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control, particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5 mg/day. At the time of reporting the events were ongoing.

The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757

DIABETES, KETOACIDOSIS.

A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750 mg daily for psychosis since November 1997. He was receiving acamprosate, depixol and priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.

The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218

DIABETES DURING PREGNANCY

Patient developed diabetes during pregnancy and started insulin on 30 September 1999. Baby due 06 December 1999, but patient's water broke 30 September 1999 and baby born in October 1999. See case 1999AP06076.

Case Number: 1999AP02989

DIABETES MELLITUS

This patient started treatment with SEROQUEL on 13 November 1998 and with fluoxetine on 12 November 1998. Urine and blood tests on 26 November 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985

NON INSULIN DEPENDENT DIABETES

A physician reported that a 44 year male patient was given SEROQUEL 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting SEROQUEL, the patient developed non-insulin dependent diabetes. SEROQUEL was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554

CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.

A report has been received from a physician concerning a 58 year old male patient who received SEROQUEL 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081

HYPERGLYCAEMIA

Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 1998. Open label medication started on 14 September 1998 and ended on 26 September 1998. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844

HYPERGLYCAEMIA, DIABETES.

A report has been received from a physician concerning a male patient in his early forties who has been receiving SEROQUEL for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.

NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken SEROQUEL since July 1998. On 31 August 1998 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 October 1999: Further information reveals that the patient was receiving SEROQUEL 200 mg for a bipolar disorder since July 1998. On 31 August 1999, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. SEROQUEL was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408

HYPERGLYCAEMIA (NON-SERIOUS)

A pharmacist and a nurse reported that a male patient taking SEROQUEL developed hyperlycaemia. The pharmacist considered the event unrelated to SEROQUEL; the nurse considered the event related to SEROQUEL. The patient was also taking stelazine.

Case Number: 1998AP45979

LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR

Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with SEROQUEL, SEROQUEL dosage has been reduced from 400 to 200mg. The physician is thinking of stopping SEROQUEL altogether.

Case Number: 1998AP18089

HYPERGLYCAEMIA.

A report has been received from a physician concerning a 32 year old male patient who has been receiving SEROQUEL from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.

On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803

DIABETIC KETOACIDOSIS

A report has been received from a physician concerning a 36 year old male who has been receiving SEROQUEL in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. SEROQUEL started on 06 September 1996. The patient had recently been diagnosed with diabetes mellitus which was controlled on glucotrol. On 18 March 1997, 28 weeks after starting SEROQUEL, he was admitted to hospital with decreased level of consciousness. He had not been taking his glucotrol or SEROQUEL for 3 to 4 days prior to admission. He was given IV fluids and insulin but later developed severe acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were:

sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin and food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted SEROQUEL. The event resolved on 01 April 1997. The investigator felt that there was not a reasonable possibility that the event was related to SEROQUEL.

Case Number: 1997AP36246

UNCONTROLLED DIABETES

A report has been received from a physician concerning a 29-year old male who has been receiving SEROQUEL since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. SEROQUEL treatment was put on hold and the patients diabetes treated with humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the SEROQUEL therapy.

Case number: 1997AP35710

UNCONTROLLED DIABETES MELLITUS

A report has been received regarding a 45 year old male who has been receiving SEROQUEL as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 August 1997, 163 days after starting SEROQUEL, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.

The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874

PNEUMONIA, DIABETES, HYPERTENSION

This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with SEROQUEL as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.

The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737

DIABETES MELLITUS

This 52 year-old-female with schizophrenia was taking SEROQUEL 400 mg from 28 January 1995 as part of a clinical trial. On 31 January 1995 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April 1995, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.

This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544

AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in SEROQUEL trial on 26 September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4 November, the patient developed

symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with SEROQUEL.

Case Number: 1994AP03286

HYPERGLYCAEMIA

An investigator reported that a 53 year old female patient started taking SEROQUEL on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893

HYPERGLYCAEMIA

An investigator reported that a 45 year old male was treated with SEROQUEL beginning on 4 March 1994. Concomitant medications included zantac and haldol. The patient had no history of diabetes mellitus. He had recently stopped taking an unblinded SEROQUEL study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. SEROQUEL was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5. DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of pre-existing diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of pre-existing diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to SEROQUEL.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily SEROQUEL dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months

(median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily SEROQUEL dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to 21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking SEROQUEL 150 mg daily for 30 months. The latter report contains scant information, except the daily SEROQUEL dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient

developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

6 REFERENCES

(1) Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

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(3) Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

(4) Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

EXHIBIT 19

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

- - -

IN RE: SEROQUEL	:	CASE NO.
PRODUCTS LIABILITY	:	
LITIGATION	:	6:06-md-01769-ACC-DAB
	:	
MDL Docket No. 1769:		

- - -

May 7, 2008

- - -

C O N F I D E N T I A L

- - -

Videotape deposition of WAYNE K. GELLER, M.D. taken pursuant to notice, was held at the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, 1650 Market Street, Philadelphia, Pennsylvania 19103, commencing at 9:00 a.m., on the above date, before Linda Rossi Rios, RPR, CCR and Notary Public.

- - -

Golkow Technologies, Inc.
One Liberty Place, 51st Floor
1650 Market Street
Philadelphia, Pennsylvania 19103
877.370.3377

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Dorothee Wientjens...," I'm sure I'm mispronouncing that, "...to respond to the Dutch Authorities regarding quetiapine and glucose metabolism." Did I read that correctly?

A. Yes.

Q. So you knew that the information you were giving to Ms. Wientjens, if I'm pronouncing that correctly, was going to be turned over to the Dutch authorities. Right?

A. I was under the impression that it would be. However, I was responding to her request.

Q. And you understood that her request was for information she could turn over to the Dutch authorities. Right?

A. Well, again, I know that there was a request that came from Dorothee Wientjens, I believe is the way she pronounces her name, and I don't have that e-mail in front of me to answer your question with the accuracy that I would

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like to.

Q. All right, sir. And then you said, "I sent Dorothee a copy of the recent Seroquel Safety Position Paper on DM and related disorders." True? That's what you said?

A. Yes. And, again, I was referring to the document which was termed a position paper, which had -- was unofficial and, in fact, was not a position paper on this topic.

MR. ALLEN: Sir, object to that as nonresponsive.

BY MR. ALLEN:

Q. You refer to it as a "Seroquel Safety Position Paper on DM and related disorders." Right?

A. Again, to make sure that we're taking this in the right -- in the correct context, this so-called Seroquel safety position paper, as it was titled, was not, in fact, an official company document and did not reflect our view and our knowledge of diabetes at that time,

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sir.

MR. ALLEN: Okay. Object to that as nonresponsive.

BY MR. ALLEN:

Q. And then you go on and you apologize. What are you apologizing for, sir?

A. Well, being relatively new to the company, it occurred to me, right afterwards it was brought to my attention that Ms. Wientjens' request appropriately should have gone through the global regulatory affairs director who then should have contacted myself and others in order to respond to the Dutch regulatory agency.

Q. So you made a mistake by letting the safety position paper go out to the regulatory authorities?

MR. RABER: Objection to form.

BY MR. ALLEN:

Q. Sir?

A. I made a mistake by

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submitting a document which was not correct, number one. And number two, I did so through an individual that was someone who I should not have given the document directly to.

Q. Who -- what department did Dorothee work in?

A. I don't know.

Q. Who was she?

A. I don't know.

Q. Okay. But Exhibit 17 is a document that you believe, at least you believe this is one of the documents that the Dutch authorities received in advertently. Is that correct?

A. I believe this is the document.

Q. You believe it is this document. Thank you, sir.

We got this from y'all's files and you authored Exhibit 17, did you not?

A. Yes, I did.

Q. And do you agree with the

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fact that based upon your review of the information you had available, if you look on page 11, the last page, do you agree --
A. I'm sorry, 11 out of --
Q. Yes, sir, I see that. It's the last page. Are you at the last page?
A. Yes.
Q. Do you agree with the statement that you drafted, "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals." Do you agree with that statement?
A. No, I disagree with that statement, sir.
Q. Okay. Why did you write it?
A. That statement was an artifact of an earlier discussion document which was a draft discussion document for the June 2000 SERM, and did

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not reflect my view of diabetes at the time that I presented at SERM in June of 2000.
Q. Well, in fact -- so you were the presenter at SERM in June of 2000?
A. Yes, I said that previously.
Q. Was Dr. Brecher there?
A. He was on the telephone, I believe.
Q. Did you in June of 2000 as presenter specifically state that Seroquel may cause impaired glucose regulation in some individuals? Isn't that what you did at that meeting?
MR. RABER: Object to the form.
BY MR. ALLEN:
Q. Isn't that what you said?
A. I think to be absolutely correct, I need to see a copy of the discussion document that was circulated for the June 2000 SERM.
Q. Now, when did you prepare Exhibit 17, sir? After the SERM meeting,

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isn't it, in June of 2000 you prepared this?
A. Exhibit 17 would have been prepared sometime in the fall of 2000, I believe.
Q. If the database that we have that was given to us in the production says this document was dated August the 10th, 2000, does that sound about right to you?
A. No, it doesn't.
Q. Can you give me or the jury any help by telling us why that database which we were provided which said August the 10th, 2000, is incorrect?
MR. RABER: Object to the form.
THE WITNESS: It certainly would not have coincided with the request on the MEB. However, I failed to consider the possibility that I started to prepare a position paper after the June SERM that discussed the issue of

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diabetes mellitus and Seroquel therapy. And, in fact, I recall specifically using as a template a draft discussion document which contained the same language that you just read, sir.
BY MR. ALLEN:
Q. And by the way, sir, that's not a true statement, that there are no reports of positive dechallenges, that's just not a true statement, is it?
MR. RABER: Objection to form.
BY MR. ALLEN:
Q. There's positive dechallenges throughout the adverse experience database in regard to Seroquel and diabetes and hyperglycemia, aren't there, sir?
MR. RABER: Objection to form.
THE WITNESS: I can state that when the discussion document was prepared, which would have

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been in May, roughly May of 2000, that that statement was correct and accurate.
BY MR. ALLEN:
Q. You also on that same -- at or about that same time, prepared -- following the June 2000 SERM meeting, you prepared Exhibit 18, the justification --
MR. RABER: Hang on. You said we were going to do one more document --
MR. ALLEN: Right.
MR. RABER: -- and we were going break.
MR. ALLEN: Yes, sir. And I'm wrong because based upon his answer, there's one more question I want to ask about Exhibit 18.
MR. RABER: I just want to know when we're going to break?
MR. ALLEN: And I told you my best --
MR. RABER: You told me and you told me wrong.

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MR. ALLEN: I was mistaken. I did not know the witness' answer. And I'm showing him Exhibit 18. I'm not trying to cause any trouble. And I'd ask him to look at Exhibit 18, which is a justification document that he also prepared concerning reasonable evidence and then we will be done.
- - -
(Exhibit Geller-18, Justification Document, was marked for identification.)
- - -
BY MR. ALLEN:
Q. Sir, I'm handing you what's been marked as Exhibit 18, which is another document from the database that you said was prepared by you on or about August the 10th, 2000. Did you prepare this justification document on Seroquel and weight gain?
A. I am listed as the author in

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the document. However, I wish to point out that this document, too, is a draft document.
MR. ALLEN: Yes, sir.
Object to that as nonresponsive.
BY MR. ALLEN:
Q. Sir, did you prepare Exhibit Number 18?
A. My name is listed as the author on this document, and I recognize the fact that it is a draft that I prepared.
Q. Yes, sir. Okay. And by the way, did you review Exhibit 17 in preparation for your deposition?
A. Yes.
Q. And you've already testified you reviewed Exhibit 16 in preparation for your deposition, or not, I can't recall, to be honest with you?
A. Yes, I believe so.
Q. Did you -- have you reviewed Exhibit 18 in preparation for your deposition? The justification document

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on Seroquel and weight gain.
A. I don't believe I have.
Q. Okay. Now, you've already testified earlier today any documents you reviewed in preparation for your deposition in this -- these 15 or 20 volumes occurred during the time you were meeting with counsel. Right?
A. Yes.
Q. You never reviewed these documents outside of the presence of counsel. Correct?
A. Correct.
Q. Okay. All right, sir. And in the justification document on Seroquel and weight gain you wrote, Exhibit 18, didn't you also state that "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can produce significant weight gain in select individuals. The Seroquel CDS mentioned the possibility of 'limited' weight gain associated with Seroquel

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safety position paper draft prepared by you, and let's -- let me stop here and it's my fault. You started working in the safety surveillance department of AstraZeneca in May of 2000. Is that correct?

A. Actually in April.

Q. I'm sorry, April. So in other words, your conclusions that we've seen in regard to weight gain, you were able to reach those conclusions between the time you started working in April and by the time you prepared the document. True?

A. The document was prepared in -- for the June SERM, which meant that that data was looked at between my join -- in the time between my joining the company and the discussion document.

Q. Thank you, sir. Now, in this Exhibit 17, safety position paper, you state, Safety data derived from clinical trials and spontaneous reports often containing limited information may

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represent a weak signal linking Seroquel with impaired glucose regulations -- regulation, including occasional reports of new onset diabetes mellitus. None of these reports are absolutely steadfast (i.e., there are no clear index cases and there were no reports of positive dechallenges/rechallenges) and most have either incomplete information or other explainable causes. Although the number of reports is fairly sizable, it was felt that there is insufficient evidence at present to warrant an amendment to the Seroquel Core Data Sheet. Did I read that correctly?

A. Yes.

Q. You go on to state, "However, it was agreed that the topic will be kept under ongoing review and will be reassessed at a later time." Did I read that correctly?

A. Yes.

Q. Why did you say the number of reports is fairly sizable?

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A. Well, it was my impression at the time that we conducted our pre-SERM activities, which would have been sometime in May 2000, that relatively speaking, that meeting, looking at a frequency table of all adverse events that had been reported in the postmarketing realm in the serious clinical trial adverse event reports, that compared to, for instance, compared to bone fractures, for instance, that the numbers seem fairly sizable. However, I have to confess that at that particular time, I had no idea how many patients had been exposed to Seroquel. So it was a statement of relative comparison, sir.

Q. Of course, when the document we saw yesterday was prepared to the FDA, you did not tell the FDA, you being AstraZeneca, that you had a fairly sizable number of diabetes cases, did you?

A. We presented all the data that we had from all sources, including

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clinical trial sources, including the literature, including the postmarketing sources that were contained in this particular document. So in answer to your question, I believe we provided them with more than what was provided here.

MR. ALLEN: Objection. Nonresponsive.

BY MR. ALLEN:

Q. You did not tell the FDA that the number of adverse experience reports concerning diabetes mellitus, you did not use the term that they were fairly sizable, did you, sir?

A. Sir, FDA requested the data. We provided them with every piece of data they requested. We provided them with our own analysis. And I have to confess that once I learned what the exposure, meaning how many patients had been exposed to Seroquel, which would have happened sometime between the preparation of the draft discussion document, from which this was based, until the SERM, it

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became apparent to me that the number of cases -- of reported cases of diabetes was not so sizable.
Q. In fact, you not only did not tell the FDA that there was a fairly sizable number of reports, you told the FDA, you being AstraZeneca, that there were very few cases of diabetes mellitus, didn't you?
A. I don't recall that specifically, sir.
Q. If it's reflected in the document that you provided to the FDA, you don't recall reviewing that document in preparation for your deposition?
A. I reviewed the document. I don't have photographic memory unfortunately, sir.
Q. I don't expect you to. And I'm just asking you whether or not -- and no one has a -- well, some people have some photographic memory. Some people do. But do you recall in reading the document that your company submitted to

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the FDA in August of 2000, that your company told the FDA that there were very few cases of diabetes mellitus and hyperglycemia? Do you recall that or not?
A. I don't recall that. However, I know that at the time we submitted the document to FDA, we had exposure figures to put -- to put these number of reports into context.
Q. Do you recall that when your company submitted the document to the MEB in January of 2001, your company told the MEB that there was a relatively small number of postmarketing reports of glucose dysregulation? Do you recall that?
A. I don't recall the specific language, sir.
Q. Nevertheless, you would agree that in the documents you prepared, the safety position paper, Exhibit 17, that you prepared, you said that the number of reports is fairly sizable? Do

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you agree with that?
A. This draft so-called safety position paper does indeed contain that statement, and, again, was written without having any contextual information as far as exposure was concerned.
Q. Now, at the last page of Exhibit 17, the safety position paper that was prepared by you, do you see the final paragraph?
MR. RABER: Object to form.
THE WITNESS: Yes.
BY MR. ALLEN:
Q. And you state, do you not, sir, While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest -- let me start again.
You state in writing, "While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes

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mellitus in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet based upon postmarketing and clinical trial safety data." That's your language, is it not, sir?
A. Yes.
Q. Was diabetes -- and do you agree with that statement, by the way, that you wrote?
A. No, I completely disagree with that statement. As I indicated yesterday, this statement was an artifact from a draft discussion document which was not the basis for the June 2000 SERM discussion document. So this was my -- this happened to be the statement which I felt was not factually correct in this document.
Q. Now, did you testify that -- let me come back to that in a minute.
So your testimony at this juncture is that final paragraph Exhibit -- of Exhibit 17, which says that

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Q. That's right.
A. No.
Q. Did you rewrite -- strike that. Let me back up.
I think you said that you used as a template for Exhibit 17 an older draft of a discussion document; is that right?
MR. PIRTLE: Objection, form.
THE WITNESS: Yes, I did.
BY MR. RABER:
Q. And is --
To the best of your knowledge, is Defendant's Exhibit 202 the template that you used when preparing Exhibit 17?
MR. PIRTLE: Objection to form.
THE WITNESS: Yes, it is.
BY MR. RABER:
Q. It appears if you look at Geller Exhibit 17, the one on the right, that you rewrote that summary and

Page 1122

conclusions paragraph; is that right?
A. Yes.
Q. Did you rewrite the last paragraph on Defendant's Exhibit 17 -- I mean Geller Exhibit 17?
A. No. It's exactly the same as the one in Defense Exhibit 202.
Q. When you say you made a mistake, is that the mistake you made, by leaving in that paragraph from this old template?
A. Yes, it is.
Q. Did the paragraph that got left in by mistake accurately reflect what had happened at the SERM meeting in June of 2000?
MR. PIRTLE: Objection to the form.
THE WITNESS: No, absolutely not.
BY MR. RABER:
Q. As we sit here today, do you recall whether or not you ever completed a final safety position paper after the

Page 1123

June 2000 SERM?
A. I don't recall there being a final position paper.
Q. Can you explain why you don't recall one of those final documents existing?
A. It is my belief, as was then, that the FDA document, which was prepared at the same time that the initial discussion document was being written, that that FDA response document really served exactly the same purpose of a position paper in that it provided all the necessary information to the reader to see that there was insufficient evidence to suggest a causal relationship between Seroquel therapy and diabetes.
Q. And in the fall of 2000, did you have another SERM meeting coming up to consider this glucose and diabetes issue again?
A. Yes.
Q. Were you drafting documents relating to that?

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A. Yes.
Q. What were you drafting in preparation for that?
A. I was drafting an update -- a new discussion document, but it was updated from the previous one with new data.
Q. Did anybody at AstraZeneca need to have a safety position paper relating to the June SERM to take any action of any kind?
MR. PIRTLE: Objection, speculation.
THE WITNESS: No, not at all.
BY MR. RABER:
Q. If SERM is going --
If there's going to be a change in the core data sheet, what kind of document gets prepared, a justification document or a safety position paper?
A. A justification document, which sometimes now goes under the name

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of a clinical overview.
Q. All right.
Dr. Geller, I want to just talk about a few more things here. I want to have you keep Geller Exhibit 17 in front of you, and I also want to show you Geller Exhibit 30.
Now, you've testified in response to questions that you believe that Geller Exhibit 17, which is also attached to Geller Exhibit 30, is a draft of a position paper; is that right?
MR. PIRTLE: Objection to the form.
THE WITNESS: Yes. I already alluded to that, I believe, in my testimony.
BY MR. RABER:
Q. Do you recall yesterday when Mr. Pirtle leaned forward in his chair and said, I don't believe you that it's a draft. Do you remember that?
A. I do, sir.
MR. PIRTLE: Form.

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BY MR. RABER:
Q. I want to talk with you a little bit about why you believe that this safety position paper that's in front of you was not a final document. Okay?
A. Yes.
Q. All right.
Let's look at Exhibit 17, Geller Exhibit 17.
If you look at the page numbering on the bottom, do you see that?
A. Yes.
Q. What do you see when you look at the page numbering on the bottom?
A. I see in this case "Page 2 of ?."
Q. What does the presence of a question mark in the page numbering indicate to you about whether or not that is a final document?
A. It indicates that it is not a final document. It indicates that it is a draft.

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Q. In fact, the preliminary draft of your June discussion document, I think it's Defense Exhibit 202, can you tell us whether or not that draft has question marks in the page numbering?
A. Yes. This says "Page Auto," A-U-T-O, separate word "Page," P-A-G-E, "of?"
Q. Now does --
Is there any question in your mind that Defense Exhibit 202 is a draft document?
A. I'm sorry. Please repeat the question.
Q. Is there any question in your mind that that's a draft?
A. There's no question, sir.
Q. All right.
Does the word "draft" appear anywhere on Defense Exhibit 202?
A. No.
Q. Let's go back, then, to Geller Exhibit 30, which is the e-mails with your draft position paper attached.

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In your e-mail, you write to Janet Spiers attaching a "position paper and justification document for diabetes, et cetera and weight gain."
Do you see that?
A. Yes.
Q. Then you say "Vikram." Who is Vikram?
A. Vikram is Vikram Dev, who was my supervisor at the time.
Q. "Vikram has not reviewed either document as his father recently passed away and he is in India."
Do you see that?
A. I'm sorry. Can you please tell me the page number?
Q. Please look at the very first page, the e-mail from you -- at the bottom from you to Janet.
A. Here we go. I'm sorry. Yes.
Q. "Vikram has not reviewed either document as his father recently passed away and he is in India."

EXHIBIT 2

AstraZeneca Pharmaceuticals

Seroquel™
(Quetiapine)

Commercial Support Team - Technical Document (TD004)

BPRS meta-analysis

Request From:

Date Requested:

Statistician/Statistical Programmer Responsible: Rob Hemmings / Karen Melvin

1 Source of Data

Data for these analyses comes from mdata.bprs (a dataset stored in the CDE within the CST directory). This is a pooled dataset of 12 trials, each of which had either BPRS or PANSS as an endpoint. These trials represent all available data on BPRS scores from the Seroquel clinical trial program.

The creation of this dataset (handling of missing data, timing of endpoint etc.) is described in a document produced by Karen Melvin. This document is held in S:\d5077zfiles\cst\dataset creation.doc.

2 Design of Trials/ Analysis Methods

2.1 Study Design

Ten studies were selected to be used in this analysis, these are listed below:

5077IL/0004, 5077IL/0006, 204636/0007, 204636/0008, 5077IL/0013, 5077IL/0014, 5077IL/0050, 5077IL/0052, 5077IL/0053, 5077IL/0054.

The two trials omitted from the original dataset were trials 5077IL/0012 and 5077IL/0015. The former because there was no internal comparator (making model fitting difficult) and the latter because of significantly different entry criteria.

In 5 of these 10 trials, the BPRS questionnaire was used as an endpoint in the trial. In the remaining 5 trials, BPRS scores have been derived from the PANSS questionnaire which was a trial endpoint.

Comparators
The analyses performed compare Seroquel separately with each of placebo; Haloperidol; Chlorpromazine; Risperidone and 'other typicals' (defined as either Haloperidol or Chlorpromazine). Four of the trials contained comparative data against placebo; 4 against Haloperidol; 2 against Chlorpromazine; 1 against Risperidone and 6 against 'other typicals'.

Seroquel Dose

A range of doses of Seroquel were used in the above-mentioned studies, therefore each comparison was performed twice with respect to level of Seroquel dose. The first used all patients receiving therapeutic doses of Seroquel (150-750mg/day - labeled 'all doses'), the second used only patients receiving high-dose Seroquel (at least 400 mg/day - labeled 'high dose').

Categories of BPRS

The 18 point BPRS scale can either be assessed as a whole or can be sub-divided into separate item or factor scores. Assessed in these analyses were:

- Factor I (Somatic concern; Anxiety; Guilt feeling; Depressive mood) - baseline ≥ 8;
- Factor V (Hostility; Suspiciousness; Uncooperativeness) - baseline ≥ 6;
- Mood Cluster (Depressive mood; Anxiety; Guilt feelings; Tension) - baseline ≥ 8;
- Hostility Cluster (Anxiety; Tension; Hostility; Suspiciousness; Uncooperativeness; Excitement) - baseline ≥ 12;
- Hostility Item - baseline ≥ 3;
- Anxiety Item - baseline ≥ 3;
- Total BPRS score - baseline ≥ 36.

Patient Population

Though each of the above-mentioned trials may have slightly different patient populations, they were considered suitable for inclusion to this meta-analysis.
For inclusion to the analysis of each of the above categories, patients were required to be symptomatic in that category. Therefore, patients were not included in the analysis of a particular category unless their baseline score was at least that denoted above (note baselines are denoted as totals within each category). In addition, patients were excluded if their disease type did not match that recognised for Seroquel use in Europe.

2.2 Analysis Methods

Two endpoints were assessed in this meta-analysis.

Firstly, a 'change from baseline' score. This was calculated separately for each category and analysed via analysis of covariance (ANCOVA) using PROC MIXED in SAS, with the baseline appropriate to that category included in the model as a covariate. A term was also included in the model for 'trial'. Also assessed were trial*treatment and covariate*treatment interactions, though these were subsequently dropped from the model unless a consistent pattern of significance of these terms could be identified across each of the endpoints assessed. The standard checks of normality assumptions behind ANCOVA were performed.

Secondly the 'proportion of responders' was analysed. A responder was defined as any patient with at least a 40% drop in score from baseline to endpoint. These data were analysed using PROC GENMOD in SAS. The model used was similar to that described for the change from baseline endpoint above.

For each endpoint, both an 'observed cases' (OC) and a 'last value carried forward' (LVCF) analysis was performed.

In total, this BPRS meta-analysis has involved 7 categories of the BPRS scale, each to be assessed against 5 comparators, using 2 endpoints, each derived in two different ways (OC and LVCF). Each analysis was then performed for 2 cuts of the SEROQUEL data (by mean dose received). This makes a total of 280 separate p-values being generated. By chance alone we expect 1 in 20 p-values to be significant, therefore isolated significant p-values will be ignored, instead interpretation of the analyses will look for patterns of significant results, either across particular categories of the BPRS or against particular comparators.

2.3 Details of SAS programs

All analysis programs are stored in the CDE under the CST directory (s:\d5077\filesm\CST).

The programs used to create the mdata.bprs dataset are described in Karen's document. The programs performing the statistical analyses are:

- TD4_X1 - change from baseline analysis;
- TD4_X1A - change from baseline analysis (high doses of SEROQUEL);
- TD4_X1B - change from baseline analysis ('other typicals');
- TD4_X1C - change from baseline analysis (high dose of SEROQUEL versus 'other typicals);
- TD4_X2 - proportion of responders;
- TD4_X2A - proportion of responders (high doses of SEROQUEL);
- TD4_X2B - proportion of responders ('other typicals');
- TD4_X2C - proportion of responders (high dose of SEROQUEL versus 'other typicals).

In addition to this, baseline scores were investigated to ensure that BPRS scores derived respectively from BPRS and PANSS questionnaires could be combined. The programs producing these baseline plots are: TD4_BASE; TD4_2BAS.

3 Results

As described above, a very large number of analyses have been performed on these data, so the results of the analyses will necessarily be described in general terms. Initially, significant results will be discussed. Any trends observed in the data will then be highlighted.

<u>Change from baseline</u>

In each of the 7 categories, Seroquel proved to be significantly better than placebo (regardless of whether 'all doses' or only high-doses of Seroquel were used). In each case this improvement was observed using an LVCF approach, however for total

BPRS score using all Seroquel data, this result was supported by the observed cases analysis.
The pattern was less obvious when Seroquel was compared with Haloperidol. Against 'all doses' of Seroquel, each of the 3 significant p-values generated was in favour of Haloperidol (Total BPRS, Factor V and Hostility Cluster). There was no evidence of significant differences between the treatments when Haloperidol was compared to high-dose Seroquel.
No statistically significant differences were observed for any of the categories when Seroquel was compared with Chlorpromazine.
Comparisons against Risperidone used only trial 5077IL/0053. Against 'all doses' of Seroquel, Risperidone showed significant improvement on Factor V scores and the Hostility Cluster. Against high-dose Seroquel only, these two categories were again significantly in favour of Risperidone, along with the Anxiety Item, Total BPRS and the Mood cluster.
Against either Chlorpromazine or Haloperidol, LVCF analyses showed a significant improvement against Seroquel for Total BPRS, Factor V and the Hostility Cluster, though these differences were removed when assessing high-dose of Seroquel only.

For 'all doses' of Seroquel, trends were observed for the Factor I cluster in which a positive, though non-significant estimate of treatment effect was observed. This was also true for the Mood cluster (with the exception of comparisons versus Risperidone). For high doses of Seroquel, the Factor I cluster again showed mainly positive treatment effects (excepting Risperidone), however no trends were apparent in any of the other categories.

A full set of results, showing least square mean changes from baseline for each treatment group, an estimate of treatment effect (difference in lsmeans) with 95% confidence interval and associated p-value are presented in Appendix A.

Proportion of responders

Seroquel ('all doses') proved to be significantly better than placebo for 4 of the 7 categories as assessed by this endpoint (total BPRS, Factor V, Hostility Cluster, Mood Cluster) and tended toward significance in the Anxiety and Hostility items. A very similar pattern was observed for high doses of Seroquel only against placebo. In each of the 4 cases the improvement was observed using an LVCF approach.
The pattern was less obvious when Seroquel was compared with Haloperidol. Against 'all doses' of Seroquel, only Factor V showed a significant difference between the treatments - in favour of Haloperidol. As for the change from baseline analysis, this difference disappeared when comparing against only high-doses of Seroquel.
Again, no statistically significant results were obtained when Seroquel was compared with Chlorpromazine.
Comparisons against Risperidone using all doses of Seroquel showed significant improvement for Risperidone on total BPRS, Factor V scores and the Hostility Cluster. Against high-dose Seroquel only, the Anxiety item, Factor I and Mood cluster scores were also significantly in favour of Risperidone.
Against either Chlorpromazine or Haloperidol, LVCF analyses showed a significant improvement against 'all doses' of Seroquel for Factor V, though this difference were removed when assessing high-dose of Seroquel only.

As above, the more positive trends for Seroquel were observed on the Factor I and Mood cluster items, though no significant differences were found in favour of Seroquel other than against placebo.

A full set of results, showing percentage of responders for each treatment group, odds ratios and 95% confidence intervals with associated p-value are presented in Appendix A.

The following table is an attempt to simplify the claims that could be obtained from these results. A ✓ is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or using LVCF. A ✗ marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

Table 1

Comparator	Category						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✗	-	✗	-	✗	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✗	✗	✗	✗	-	✗	✗
Other typicals	-	✗	-	✗	-	✗	-

4 Conclusions

In terms of generating positive claims for Seroquel, these analyses seem somewhat disappointing. Although some trends in favour of Seroquel were observed in the Factor I and Mood cluster items, there was no evidence in these analyses of a significant benefit for using Seroquel over any other of the active agents assessed. There was, however, consistent evidence that Seroquel is better than placebo for a number of the BPRS sub-categories assessed.

There was little evidence of improvement with high-doses of Seroquel relative to including 'all doses' of Seroquel, though in the Haloperidol studies some of the statistically significant disadvantages were removed when looking at high doses only. In contrast, in the comparisons against Risperidone (trial 5077IL/0053), looking at high doses of Seroquel appears to give relatively worse results than looking at all patients together.

In general, the analysis of the two endpoints of mean change from baseline and proportion of responders gave similar conclusions.

5 References

No references were used.

Appendix A: Statistical Appendix

Index of Tables Created

TITLE

Key: VAR - Category of BPRS being assessed (Anxiety Item, Total BPRS; Factor I; Factor V; Hostility Item; Hostility Cluster; Mood Cluster).
COMP - Comparator
LSCOMP - least square mean of comparator
LSSER - least square mean of Seroquel
EST - Estimate of treatment effect (either difference in lsmeans or odds ratio)
P_T - p-value
LOWER / LCL - 95% lower confidence interval bound
UPPER / UCL - 95% upper confidence interval bound
ANAL - OBSERVED CASES or LVCF analysis
SIG - * denotes statistical significance
SERN - Number of patients on Seroquel
SERR - Number of responders on Seroquel
SER% - Percentage of responders on Seroquel
COMPN - Number of patients on comparator
COMPR - Number of responders on comparator
COMP% - Percentage of responders on comparator

TABLE T1 Change from baseline analyses - all doses of Seroquel

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	ANAL	SIG
1	-1.92888240	ENDANX	PLA	-2.16321932	0.23433692	0.2397	-0.1574	0.6261	OBSERVED CASES	
2	-1.22148681	ENDANX	PLA	-1.65696543	0.43547863	0.0070	0.1198	0.7512	LVCF	*
3	-1.64311081	ENDANX	HAL	-1.81583045	0.17271963	0.2842	-0.1441	0.4895	OBSERVED CASES	
4	-1.09703883	ENDANX	HAL	-1.23353560	0.13649677	0.3027	-0.1234	0.3964	LVCF	
5	-1.87706692	ENDANX	CHL	-1.80553924	-0.07152768	0.7017	-0.4395	0.2964	OBSERVED CASES	
6	-1.52013169	ENDANX	CHL	-1.47974816	-0.04038353	0.8284	-0.4070	0.3263	LVCF	
7	-1.96801427	ENDANX	RIS	-2.00028493	0.03227066	0.8844	-0.4066	0.4712	OBSERVED CASES	
8	-1.46212777	ENDANX	RIS	-1.38227098	-0.07985680	0.7155	-0.5116	0.3518	LVCF	
9	-17.76054585	ENDBPRS	PLA	-24.83229285	7.07174700	0.0039	2.2999	11.8436	OBSERVED CASES	*
10	-3.29219461	ENDBPRS	PLA	-12.10226823	8.81007362	0.0001	5.4671	12.1531	LVCF	*
11	-20.50075645	ENDBPRS	HAL	-19.87384433	-0.62691212	0.6831	-3.6447	2.3909	OBSERVED CASES	
12	-13.24621220	ENDBPRS	HAL	-9.93053659	-3.31567561	0.0145	-5.9713	-0.6600	LVCF	*
13	-22.13053657	ENDBPRS	CHL	-21.67375945	-0.45677712	0.8012	-4.0275	3.1139	OBSERVED CASES	
14	-17.75196333	ENDBPRS	CHL	-17.26124270	-0.49072063	0.7930	-4.1681	3.1867	LVCF	
15	-23.87001671	ENDBPRS	RIS	-24.11188221	0.24186550	0.9019	-3.6315	4.1152	OBSERVED CASES	
16	-19.45877126	ENDBPRS	RIS	-16.29780780	-3.16096346	0.1581	-7.5608	1.2388	LVCF	
17	-5.97958774	ENDFI	PLA	-6.95215090	0.97256316	0.1030	-0.1984	2.1435	OBSERVED CASES	
18	-3.75138902	ENDFI	PLA	-5.26858020	1.51719118	0.0024	0.5412	2.4932	LVCF	*
19	-5.01792808	ENDFI	HAL	-5.52521580	0.50728772	0.2369	-0.3349	1.3495	OBSERVED CASES	
20	-3.20544661	ENDFI	HAL	-3.47503972	0.26959311	0.4574	-0.4425	0.9817	LVCF	
21	-5.59177074	ENDFI	CHL	-6.35956050	0.76778976	0.1385	-0.2509	1.7865	OBSERVED CASES	
22	-4.60027853	ENDFI	CHL	-5.12941442	0.52913590	0.3319	-0.5437	1.6019	LVCF	
23	-5.15051726	ENDFI	RIS	-5.96312710	0.81260984	0.2096	-0.4636	2.0888	OBSERVED CASES	
24	-4.25134959	ENDFI	RIS	-4.29459640	0.04324681	0.9417	-1.1229	1.2093	LVCF	
25	-3.39572940	ENDFV	PLA	-4.46652537	1.07079596	0.0867	-0.1559	2.2974	OBSERVED CASES	
26	-1.35968707	ENDFV	PLA	-3.06318005	1.70349297	0.0003	0.7818	2.6252	LVCF	*
27	-4.32580592	ENDFV	HAL	-4.09406696	-0.23173895	0.4981	-0.9038	0.4403	OBSERVED CASES	
28	-3.04323303	ENDFV	HAL	-1.67985602	-1.36337701	0.0001	-2.0111	-0.7157	LVCF	*
29	-4.94827119	ENDFV	CHL	-4.54810579	-0.40016540	0.3761	-1.2899	0.4896	OBSERVED CASES	
30	-3.68675735	ENDFV	CHL	-3.42537388	-0.26138347	0.5942	-1.2262	0.7034	LVCF	
31	-5.54643474	ENDFV	RIS	-4.64890205	-0.89753268	0.0453	-1.7758	-0.0192	OBSERVED CASES	*
32	-4.12803635	ENDFV	RIS	-2.76431072	-1.36372563	0.0113	-2.4150	-0.3124	LVCF	*
33	-1.24805589	ENDHOST	PLA	-1.63088616	0.38283027	0.2615	-0.2898	1.0555	OBSERVED CASES	
34	-0.46937795	ENDHOST	PLA	-1.05716657	0.58778862	0.0155	0.1129	1.0627	LVCF	*
35	-2.09204701	ENDHOST	HAL	-2.17564885	0.08360184	0.7463	-0.4267	0.5939	OBSERVED CASES	
36	-1.56003798	ENDHOST	HAL	-1.17563778	-0.38440019	0.1020	-0.8457	0.0769	LVCF	
37	-2.14402246	ENDHOST	CHL	-2.13340168	-0.01062078	0.9632	-0.4658	0.4445	OBSERVED CASES	
38	-1.70533282	ENDHOST	CHL	-1.58320219	-0.12213063	0.6438	-0.6430	0.3987	LVCF	

39	-2.38373083	ENDHOST	RIS	-2.27768313	-0.10604770	0.7365	-0.7367	0.5246	OBSERVED CASES	
40	-2.02228254	ENDHOST	RIS	-1.40345663	-0.61882591	0.1169	-1.3966	0.1590	LVCF	
41	-7.58622096	ENDJMCK	PLA	-9.20592510	1.61970414	0.1167	-0.4079	3.6473	OBSERVED CASES	
42	-1.58099388	ENDJMCK	PLA	-4.56653108	2.98553719	0.0002	1.4067	4.5644	LVCF	*
43	-7.81202611	ENDJMCK	HAL	-7.60864672	-0.20337939	0.7424	-1.4194	1.0127	OBSERVED CASES	
44	-4.81841620	ENDJMCK	HAL	-3.50475023	-1.31366597	0.0267	-2.4748	-0.1526	LVCF	*
45	-9.48084330	ENDJMCK	CHL	-8.21072808	-1.27011522	0.1128	-2.8427	0.3024	OBSERVED CASES	
46	-7.06886652	ENDJMCK	CHL	-5.94149790	-1.12736863	0.2196	-2.9311	0.6764	LVCF	
47	-10.06303733	ENDJMCK	RIS	-8.79758485	-1.26545248	0.1184	-2.8576	0.3267	OBSERVED CASES	
48	-7.72743912	ENDJMCK	RIS	-4.78555086	-2.94188826	0.0022	-4.8135	-1.0702	LVCF	*
49	-6.06556776	ENDMOOD	PLA	-6.74951208	0.68394433	0.2579	-0.5051	1.8730	OBSERVED CASES	
50	-3.12900293	ENDMOOD	PLA	-4.94488213	1.81587920	0.0001	0.8876	2.7442	LVCF	*
51	-5.02980482	ENDMOOD	HAL	-5.45043252	0.42062770	0.3317	-0.4306	1.2719	OBSERVED CASES	
52	-3.19803087	ENDMOOD	HAL	-3.29500962	0.09697875	0.7915	-0.6231	0.8171	LVCF	
53	-6.02250350	ENDMOOD	CHL	-6.43589786	0.41339435	0.4230	-0.6031	1.4298	OBSERVED CASES	
54	-4.94702421	ENDMOOD	CHL	-5.01676714	0.06974293	0.9007	-1.0306	1.1701	LVCF	
55	-5.80608660	ENDMOOD	RIS	-6.24701590	0.44092930	0.4473	-0.7039	1.5857	OBSERVED CASES	
56	-4.58206556	ENDMOOD	RIS	-4.48510122	-0.09696434	0.8646	-1.2167	1.0227	LVCF	

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	SIG	ANAL
1	-1.79389637	ENDANX	CHLOR + HAL	-1.86827025	0.07437388	0.5665	-0.1805	0.3292		OBSERVED CASES
2	-1.34183576	ENDANX	CHLOR + HAL	-1.36361603	0.02178027	0.8554	-0.2129	0.2565		LVCF
3	-21.58305415	ENDBPRS	CHLOR + HAL	-21.36233494	-0.22071921	0.8578	-2.6396	2.1981		OBSERVED CASES
4	-15.56831038	ENDBPRS	CHLOR + HAL	-12.94068905	-2.62762133	0.0302	-5.0029	-0.2524	*	LVCF
5	-5.29156414	ENDFI	CHLOR + HAL	-5.85050268	0.55893853	0.1077	-0.1227	1.2406		OBSERVED CASES
6	-3.83463775	ENDFI	CHLOR + HAL	-4.02731873	0.19268098	0.5522	-0.4435	0.8288		LVCF
7	-4.73066465	ENDFV	CHLOR + HAL	-4.46158711	-0.26907754	0.3340	-0.8158	0.2777		OBSERVED CASES
8	-3.47305920	ENDFV	CHLOR + HAL	-2.41828126	-1.05477795	0.0004	-1.6334	-0.4762	*	LVCF
9	-2.22606169	ENDHOST	CHLOR + HAL	-2.36440571	0.13834401	0.4211	-0.2001	0.4768		OBSERVED CASES
10	-1.66087953	ENDHOST	CHLOR + HAL	-1.46361825	-0.19726128	0.3046	-0.5747	0.1802		LVCF
11	-8.71122711	ENDJMCK	CHLOR + HAL	-8.08021617	-0.63101094	0.2213	-1.6435	0.3815		OBSERVED CASES
12	-6.01005250	ENDJMCK	CHLOR + HAL	-4.55178363	-1.45826887	0.0078	-2.5312	-0.3853	*	LVCF
13	-5.54239435	ENDMOOD	CHLOR + HAL	-5.92187829	0.37948394	0.2860	-0.3188	1.0777		OBSERVED CASES
14	-3.98221893	ENDMOOD	CHLOR + HAL	-3.96771977	-0.01449915	0.9658	-0.6784	0.6494		LVCF

TABLE T2 Change from baseline analyses - high doses of Seroquel only

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	ANAL	SIG
1	-1.86002641	ENDANX	PLA	-1.89606302	0.03603661	0.8789	-0.4310	0.5030	OBSERVED CASES	
2	-1.11975252	ENDANX	PLA	-1.78884859	0.66909607	0.0006	0.2921	1.0461	LVCF	*
3	-1.59109117	ENDANX	HAL	-1.64386973	0.05277856	0.7670	-0.2978	0.4033	OBSERVED CASES	
4	-1.06312514	ENDANX	HAL	-1.30147985	0.23835471	0.1093	-0.0536	0.5304	LVCF	
5	-1.89249276	ENDANX	CHL	-1.78497344	-0.10751932	0.5883	-0.4990	0.2840	OBSERVED CASES	
6	-1.54665474	ENDANX	CHL	-1.48872100	-0.05793374	0.7723	-0.4522	0.3363	LVCF	
7	-2.01077886	ENDANX	RIS	-1.34670550	-0.66407335	0.0196	-1.2188	-0.1093	OBSERVED CASES	*
8	-1.49368861	ENDANX	RIS	-1.06956530	-0.42412331	0.1523	-1.0071	0.1588	LVCF	
9	-12.37181763	ENDBPRS	PLA	-17.70516480	5.33334716	0.0633	-0.2998	10.9665	OBSERVED CASES	
10	1.92442320	ENDBPRS	PLA	-9.05845346	10.98287666	0.0001	6.9911	14.9746	LVCF	*
11	-20.60733481	ENDBPRS	HAL	-17.94615278	-2.66118203	0.1137	-5.9627	0.6404	OBSERVED CASES	
12	-13.07277770	ENDBPRS	HAL	-10.93796166	-2.13481604	0.1576	-5.0989	0.8292	LVCF	
13	-22.18010978	ENDBPRS	CHL	-21.09511723	-1.08499254	0.5766	-4.9115	2.7415	OBSERVED CASES	
14	-17.78622375	ENDBPRS	CHL	-17.94716357	0.16093982	0.9357	-3.7650	4.0869	LVCF	
15	-23.87226225	ENDBPRS	RIS	-16.11690026	-7.75536199	0.0010	-12.3094	-3.2013	OBSERVED CASES	*
16	-19.43587302	ENDBPRS	RIS	-14.03920633	-5.39666670	0.0483	-10.7530	-0.0403	LVCF	*
17	-5.33815164	ENDFI	PLA	-5.66256394	0.32441230	0.6460	-1.0717	1.7206	OBSERVED CASES	
18	-2.92912778	ENDFI	PLA	-4.78898154	1.85985376	0.0025	0.6620	3.0577	LVCF	*
19	-4.91747782	ENDFI	HAL	-5.01335594	0.09587812	0.8379	-0.8264	1.0181	OBSERVED CASES	
20	-3.14125964	ENDFI	HAL	-3.71357248	0.57231284	0.1683	-0.2429	1.3875	LVCF	
21	-5.61517512	ENDFI	CHL	-6.26132346	0.64614835	0.2370	-0.4298	1.7221	OBSERVED CASES	
22	-4.63766965	ENDFI	CHL	-5.20598269	0.56831304	0.3264	-0.5713	1.7079	LVCF	
23	-5.15138965	ENDFI	RIS	-4.17475898	-0.97663067	0.1900	-2.4464	0.4932	OBSERVED CASES	
24	-4.24152962	ENDFI	RIS	-4.07587467	-0.16565495	0.8215	-1.6166	1.2853	LVCF	
25	-2.47225948	ENDFV	PLA	-3.36632258	0.89406310	0.2675	-0.6957	2.4839	OBSERVED CASES	
26	0.05125015	ENDFV	PLA	-2.58746679	2.63871693	0.0001	1.4935	3.7839	LVCF	*
27	-4.36108417	ENDFV	HAL	-4.02115444	-0.33992973	0.3603	-1.0702	0.3904	OBSERVED CASES	
28	-2.99474409	ENDFV	HAL	-2.34345872	-0.65128537	0.0677	-1.3502	0.0476	LVCF	
29	-4.94358920	ENDFV	CHL	-4.31140900	-0.63218020	0.1962	-1.5938	0.3295	OBSERVED CASES	
30	-3.68852378	ENDFV	CHL	-3.38474114	-0.30378264	0.5655	-1.3438	0.7362	LVCF	
31	-5.57247882	ENDFV	RIS	-3.17936878	-2.39311003	0.0001	-3.4499	-1.3363	OBSERVED CASES	*
32	-4.15897803	ENDFV	RIS	-2.70767998	-1.45129805	0.0368	-2.8124	-0.0902	LVCF	*
33	-1.23889365	ENDHOST	PLA	-1.72895804	0.49006439	0.2205	-0.3017	1.2818	OBSERVED CASES	
34	-0.41106989	ENDHOST	PLA	-1.49663968	1.08556979	0.0002	0.5253	1.6459	LVCF	*
35	-2.11643366	ENDHOST	HAL	-2.13421944	0.01778577	0.9476	-0.5177	0.5533	OBSERVED CASES	

36	-1.57249014	ENDHOST	HAL	-1.52913520	-0.04335494	0.8571	-0.5178	0.4311	LVCF	
37	-2.15169346	ENDHOST	CHL	-2.08561463	-0.06607884	0.7969	-0.5743	0.4421	OBSERVED CASES	
38	-1.72271481	ENDHOST	CHL	-1.60957163	-0.11314318	0.6975	-0.6876	0.4613	LVCF	
39	-2.43329859	ENDHOST	RIS	-2.02240750	-0.41089109	0.3877	-1.3646	0.5428	OBSERVED CASES	
40	-2.02411142	ENDHOST	RIS	-1.85877596	-0.16533546	0.7800	-1.3501	1.0195	LVCF	
41	-5.60851358	ENDJMCK	PLA	-6.79468075	1.18616717	0.3366	-1.2490	3.6213	OBSERVED CASES	
42	0.15085958	ENDJMCK	PLA	-4.47356794	4.62442752	0.0001	2.7161	6.5328	LVCF	*
43	-7.94031667	ENDJMCK	HAL	-7.29773930	-0.64257737	0.3438	-1.9765	0.6913	OBSERVED CASES	
44	-4.74070420	ENDJMCK	HAL	-4.25545285	-0.48525135	0.4541	-1.7582	0.7877	LVCF	
45	-9.48625190	ENDJMCK	CHL	-7.97775099	-1.50850091	0.0808	-3.2040	0.1870	OBSERVED CASES	
46	-7.06362286	ENDJMCK	CHL	-5.97633527	-1.08728759	0.2691	-3.0210	0.8464	LVCF	
47	-10.12324070	ENDJMCK	RIS	-5.60285644	-4.52038426	0.0001	-6.4103	-2.6305	OBSERVED CASES	*
48	-7.80928475	ENDJMCK	RIS	-4.13101782	-3.67826693	0.0030	-6.0835	-1.2730	LVCF	*
49	-5.62749649	ENDMOOD	PLA	-5.45764233	-0.16985416	0.8098	-1.5648	1.2251	OBSERVED CASES	
50	-2.61444904	ENDMOOD	PLA	-4.82320777	2.20875873	0.0001	1.0947	3.3228	LVCF	*
51	-4.90700396	ENDMOOD	HAL	-4.77209872	-0.13490524	0.7806	-1.0875	0.8177	OBSERVED CASES	
52	-3.11911109	ENDMOOD	HAL	-3.62295343	0.50384234	0.2252	-0.3116	1.3193	LVCF	
53	-6.01787574	ENDMOOD	CHL	-6.34122818	0.32335243	0.5532	-0.7520	1.3987	OBSERVED CASES	
54	-4.96993289	ENDMOOD	CHL	-4.97172332	0.00179043	0.9976	-1.1695	1.1731	LVCF	
55	-5.79496411	ENDMOOD	RIS	-4.04830400	-1.74666011	0.0156	-3.1544	-0.3389	OBSERVED CASES	*
56	-4.55460111	ENDMOOD	RIS	-3.71002082	-0.84458028	0.2451	-2.2755	0.5863	LVCF	

OBS	LSCOMP	VAR	COMP	LSSER	EST	P_T	LOWER	UPPER	SIG	ANAL
1	-1.76707457	ENDANX	CHLOR + HAL	-1.75815550	-0.00891907	0.9494	-0.2852	0.2674		OBSERVED CASES
2	-1.34475999	ENDANX	CHLOR + HAL	-1.42217172	0.07741173	0.5584	-0.1823	0.3371		LVCF
3	-21.71790120	ENDBPRS	CHLOR + HAL	-20.06123241	-1.65666879	0.2168	-4.2892	0.9759		OBSERVED CASES
4	-15.71720341	ENDBPRS	CHLOR + HAL	-14.29704250	-1.42016091	0.2815	-4.0079	1.1676		LVCF
5	-5.28710769	ENDFI	CHLOR + HAL	-5.56411911	0.27701141	0.4618	-0.4626	1.0166		OBSERVED CASES
6	-3.85988690	ENDFI	CHLOR + HAL	-4.27867823	0.41879133	0.2505	-0.2964	1.1339		LVCF
7	-4.75713631	ENDFV	CHLOR + HAL	-4.33339252	-0.42374379	0.1629	-1.0197	0.1722		OBSERVED CASES
8	-3.51044253	ENDFV	CHLOR + HAL	-2.93657933	-0.57386319	0.0716	-1.1984	0.0507		LVCF
9	-2.23114003	ENDHOST	CHLOR + HAL	-2.31125371	0.08011368	0.6671	-0.2869	0.4471		OBSERVED CASES
10	-1.71941743	ENDHOST	CHLOR + HAL	-1.72362724	0.00420981	0.9832	-0.3886	0.3970		LVCF
11	-8.80937945	ENDJMCK	CHLOR + HAL	-7.77454339	-1.03483606	0.0645	-2.1320	0.0624		OBSERVED CASES
12	-6.03853602	ENDJMCK	CHLOR + HAL	-5.13024481	-0.90829122	0.1255	-2.0711	0.2545		LVCF
13	-5.54214234	ENDMOOD	CHLOR + HAL	-5.61075894	0.06861661	0.8604	-0.6982	0.8355		OBSERVED CASES
14	-4.00945108	ENDMOOD	CHLOR + HAL	-4.31670134	0.30725027	0.4142	-0.4314	1.0459		LVCF

TABLE T3 Proportion of responders - all doses of Seroquel

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	0.74012	0.36442	1.50316	0.40512	160	68	42.5000	56	24	42.8571	
2	PLA	RESPANX	LVCF	0.62955	0.38382	1.03262	0.06682	307	99	32.2476	123	35	28.4553	
3	PLA	RESPBPRS	OBSERVED CASES	0.46342	0.21431	1.00210	0.05062	148	72	48.6486	41	15	36.5854	
4	PLA	RESPBPRS	LVCF	0.34725	0.19061	0.63258	0.00055	304	87	28.6184	115	17	14.7826	*
5	PLA	RESPFI	OBSERVED CASES	0.65689	0.31573	1.36670	0.26091	141	82	58.1560	49	28	57.1429	
6	PLA	RESPFI	LVCF	0.67151	0.41248	1.09322	0.10926	261	114	43.6782	108	43	39.8148	
7	PLA	RESPFV	OBSERVED CASES	0.56606	0.28394	1.12848	0.10596	144	82	56.9444	48	22	45.8333	
8	PLA	RESPFV	LVCF	0.46766	0.28284	0.77324	0.00305	288	106	36.8056	120	30	25.0000	*
9	PLA	RESPHOST	OBSERVED CASES	2.31667	0.86413	6.21083	0.09497	79	35	44.3038	26	17	65.3846	
10	PLA	RESPHOST	LVCF	0.73154	0.39894	1.34143	0.31225	171	73	42.6901	66	26	39.3939	
11	PLA	RESPJMCK	OBSERVED CASES	0.67637	0.32345	1.41436	0.29885	141	81	57.4468	46	25	54.3478	
12	PLA	RESPJMCK	LVCF	0.53356	0.32427	0.87796	0.01343	297	103	34.6801	121	32	26.4463	*
13	PLA	RESPMOOD	OBSERVED CASES	0.60295	0.27408	1.32642	0.20849	151	88	58.2781	45	27	60.0000	
14	PLA	RESPMOOD	LVCF	0.47078	0.28393	0.78059	0.00350	284	119	41.9014	116	38	32.7586	*
15	HAL	RESPANX	OBSERVED CASES	1.10065	0.66436	1.82346	0.70965	188	96	51.0638	131	78	59.5420	
16	HAL	RESPANX	LVCF	1.00224	0.69463	1.44607	0.99046	350	128	36.5714	229	99	43.2314	
17	HAL	RESPBPRS	OBSERVED CASES	0.82711	0.52225	1.30993	0.41843	209	117	55.9809	164	96	58.5366	
18	HAL	RESPBPRS	LVCF	1.04784	0.74126	1.48120	0.79132	381	129	33.8583	262	107	40.8397	
19	HAL	RESPFI	OBSERVED CASES	0.80527	0.50046	1.29573	0.37215	185	108	58.3784	151	83	54.9669	
20	HAL	RESPFI	LVCF	0.88699	0.62842	1.25195	0.49521	352	145	41.1932	260	106	40.7692	
21	HAL	RESPFV	OBSERVED CASES	1.14320	0.70212	1.86136	0.59052	190	117	61.5789	168	118	70.2381	
22	HAL	RESPFV	LVCF	1.53737	1.08756	2.17323	0.01488	359	138	38.4401	262	145	55.3435	*
23	HAL	RESPHOST	OBSERVED CASES	0.80849	0.32541	2.00871	0.64707	71	42	59.1549	61	43	70.4918	
24	HAL	RESPHOST	LVCF	1.16633	0.63650	2.13721	0.61853	153	72	47.0588	94	59	62.7660	
25	HAL	RESPJMCK	OBSERVED CASES	0.90595	0.56277	1.45843	0.68432	197	117	59.3909	163	102	62.5767	
26	HAL	RESPJMCK	LVCF	1.02574	0.72369	1.45384	0.88646	366	136	37.1585	264	117	44.3182	
27	HAL	RESPMOOD	OBSERVED CASES	0.83245	0.52485	1.32032	0.43584	196	111	56.6327	151	82	54.3046	
28	HAL	RESPMOOD	LVCF	0.91593	0.65226	1.28618	0.61217	367	144	39.2371	262	104	39.6947	
29	CHL	RESPANX	OBSERVED CASES	0.87515	0.47998	1.59568	0.66344	98	58	59.1837	86	49	56.9767	
30	CHL	RESPANX	LVCF	1.00451	0.60414	1.67019	0.98617	124	61	49.1935	120	60	50.0000	
31	CHL	RESPBPRS	OBSERVED CASES	1.00690	0.56956	1.78005	0.98113	111	64	57.6577	109	62	56.8807	
32	CHL	RESPBPRS	LVCF	0.97390	0.60221	1.57500	0.91413	141	68	48.2270	148	70	47.2973	
33	CHL	RESPFI	OBSERVED CASES	0.78230	0.38669	1.58265	0.49465	81	59	72.8395	70	47	67.1429	
34	CHL	RESPFI	LVCF	0.87010	0.49762	1.52139	0.62549	105	61	58.0952	98	53	54.0816	
35	CHL	RESPFV	OBSERVED CASES	1.62199	0.86998	3.02405	0.12807	99	61	61.6162	100	72	72.0000	
36	CHL	RESPFV	LVCF	1.39066	0.84854	2.27915	0.19075	128	64	50.0000	142	83	58.4507	
37	CHL	RESPHOST	OBSERVED CASES	0.94059	0.38535	2.29587	0.89299	57	44	77.1930	56	42	75.0000	
38	CHL	RESPHOST	LVCF	0.95070	0.48734	1.85460	0.88211	72	48	66.6667	85	55	64.7059	

39	CHL	RESPJMCK	OBSERVED CASES	1.54632	0.83661	2.85809	0.16429	106	66	62.2642	99	70	70.7071	
40	CHL	RESPJMCK	LVCF	1.32930	0.81525	2.16749	0.25381	132	67	50.7576	141	81	57.4468	
41	CHL	RESPMOOD	OBSERVED CASES	0.86218	0.43889	1.69372	0.66687	86	61	70.9302	81	55	67.9012	
42	CHL	RESPMOOD	LVCF	1.16473	0.67777	2.00154	0.58095	111	62	55.8559	112	66	58.9286	
43	RIS	RESPANX	OBSERVED CASES	1.05654	0.48008	2.32521	0.89129	56	38	67.8571	64	45	70.3125	
44	RIS	RESPANX	LVCF	1.04980	0.58503	1.88381	0.87059	92	47	51.0870	94	50	53.1915	
45	RIS	RESPBPRS	OBSERVED CASES	2.03711	0.98478	4.21394	0.05503	67	44	65.6716	87	69	79.3103	
46	RIS	RESPBPRS	LVCF	2.26644	1.29137	3.97777	0.00436	98	47	47.9592	111	75	67.5676	*
47	RIS	RESPFI	OBSERVED CASES	1.12183	0.50245	2.50477	0.77907	55	38	69.0909	60	43	71.6667	
48	RIS	RESPFI	LVCF	1.47727	0.81762	2.66911	0.19606	91	47	51.6484	90	55	61.1111	
49	RIS	RESPFV	OBSERVED CASES	2.77949	1.17282	6.58719	0.02023	64	46	71.8750	82	72	87.8049	*
50	RIS	RESPFV	LVCF	2.26563	1.27812	4.01611	0.00511	95	49	51.5789	113	80	70.7965	*
51	RIS	RESPHOST	OBSERVED CASES	0.81567	0.17382	3.82769	0.79617	18	15	83.3333	32	26	81.2500	
52	RIS	RESPHOST	LVCF	1.22882	0.40973	3.68531	0.71308	26	18	69.2308	41	30	73.1707	
53	RIS	RESPJMCK	OBSERVED CASES	2.64135	1.19359	5.84517	0.01655	73	51	69.8630	85	73	85.8824	*
54	RIS	RESPJMCK	LVCF	2.76130	1.59364	4.78449	0.00029	115	54	46.9565	113	80	70.7965	*
55	RIS	RESPMOOD	OBSERVED CASES	0.95115	0.43766	2.06714	0.89938	64	47	73.4375	72	53	73.6111	
56	RIS	RESPMOOD	LVCF	1.17261	0.66606	2.06441	0.58109	97	53	54.6392	104	62	59.6154	

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	CHL + HAL	RESPANX	OBSERVED CASES	1.00005	0.68005	1.47063	0.99978	286	154	53.8462	217	127	58.5253	
2	CHL + HAL	RESPANX	LVCF	1.00444	0.74656	1.35139	0.97665	474	189	39.8734	349	159	45.5587	
3	CHL + HAL	RESPBPRS	OBSERVED CASES	0.89641	0.62734	1.28090	0.54817	320	181	56.5625	273	158	57.8755	
4	CHL + HAL	RESPBPRS	LVCF	1.02459	0.77376	1.35674	0.86535	522	197	37.7395	410	177	43.1707	
5	CHL + HAL	RESPFI	OBSERVED CASES	0.80208	0.54104	1.18907	0.27224	266	167	62.7820	221	130	58.8235	
6	CHL + HAL	RESPFI	LVCF	0.87916	0.65594	1.17834	0.38879	457	206	45.0766	358	159	44.4134	
7	CHL + HAL	RESPFV	OBSERVED CASES	1.32579	0.90544	1.94128	0.14721	289	178	61.5917	268	190	70.8955	
8	CHL + HAL	RESPFV	LVCF	1.48572	1.11989	1.97105	0.00605	487	202	41.4784	404	228	56.4356	*
9	CHL + HAL	RESPHOST	OBSERVED CASES	0.87307	0.46250	1.64812	0.67541	128	86	67.1875	117	85	72.6496	
10	CHL + HAL	RESPHOST	LVCF	1.06334	0.67852	1.66642	0.78875	225	120	53.3333	179	114	63.6872	
11	CHL + HAL	RESPJMCK	OBSERVED CASES	1.11128	0.76458	1.61519	0.58023	303	183	60.3960	262	172	65.6489	
12	CHL + HAL	RESPJMCK	LVCF	1.11776	0.84221	1.48346	0.44078	498	203	40.7631	405	198	48.8889	
13	CHL + HAL	RESPMOOD	OBSERVED CASES	0.84641	0.57930	1.23667	0.38870	282	172	60.9929	232	137	59.0517	
14	CHL + HAL	RESPMOOD	LVCF	0.97218	0.73004	1.29462	0.84689	478	206	43.0962	374	170	45.4545	

TABLE T4 Proportion of responders - high doses of Seroquel

OBS	COMP	END	ANAL		EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	1.00609	0.42910	2.3589	0.98887	78	29	37.1795	56	24	42.8571		
2	PLA	RESPANX	LVCF	0.55862	0.29316	1.0645	0.07671	115	35	30.4348	123	35	28.4553		
3	PLA	RESPBPRS	OBSERVED CASES	0.57553	0.24076	1.3758	0.21407	73	31	42.4658	41	15	36.5854		
4	PLA	RESPBPRS	LVCF	0.28512	0.13993	0.5810	0.00055	112	34	30.3571	115	17	14.7826	*	
5	PLA	RESPFI	OBSERVED CASES	0.95408	0.41226	2.2080	0.91256	66	33	50.0000	49	28	57.1429		
6	PLA	RESPFI	LVCF	0.62615	0.33711	1.1630	0.13836	95	41	43.1579	108	43	39.8148		
7	PLA	RESPFV	OBSERVED CASES	0.58365	0.25353	1.3436	0.20562	68	38	55.8824	48	22	45.8333		
8	PLA	RESPFV	LVCF	0.32391	0.17223	0.6092	0.00047	106	45	42.4528	120	30	25.0000	*	
9	PLA	RESPHOST	OBSERVED CASES	3.05269	0.87224	10.6838	0.08079	39	18	46.1538	26	17	65.3846		
10	PLA	RESPHOST	LVCF	0.54936	0.25287	1.1935	0.13024	64	30	46.8750	66	26	39.3939		
11	PLA	RESPJMCK	OBSERVED CASES	0.78544	0.34015	1.8136	0.57163	73	41	56.1644	46	25	54.3478		
12	PLA	RESPJMCK	LVCF	0.37059	0.20183	0.6805	0.00137	113	47	41.5929	121	32	26.4463	*	
13	PLA	RESPMOOD	OBSERVED CASES	0.94119	0.39114	2.2647	0.89238	73	35	47.9452	45	27	60.0000		
14	PLA	RESPMOOD	LVCF	0.43121	0.22746	0.8175	0.00995	104	42	40.3846	116	38	32.7586	*	
15	HAL	RESPANX	OBSERVED CASES	1.29289	0.75330	2.2190	0.35129	122	58	47.5410	131	78	59.5420		
16	HAL	RESPANX	LVCF	0.94565	0.61323	1.4582	0.80034	179	68	37.9888	229	99	43.2314		
17	HAL	RESPBPRS	OBSERVED CASES	1.04852	0.64126	1.7144	0.85019	139	70	50.3597	164	96	58.5366		
18	HAL	RESPBPRS	LVCF	0.96270	0.64271	1.4420	0.85372	196	72	36.7347	262	107	40.8397		
19	HAL	RESPFI	OBSERVED CASES	0.99822	0.59598	1.6719	0.99461	117	61	52.1368	151	83	54.9669		
20	HAL	RESPFI	LVCF	0.83100	0.55084	1.2537	0.37756	169	72	42.6036	260	106	40.7692		
21	HAL	RESPFV	OBSERVED CASES	1.16281	0.68557	1.9723	0.57577	132	80	60.6061	168	118	70.2381		
22	HAL	RESPFV	LVCF	1.20884	0.81128	1.8012	0.35127	194	89	45.8763	262	145	55.3435		
23	HAL	RESPHOST	OBSERVED CASES	0.86477	0.33671	2.2210	0.76272	52	34	65.3846	61	43	70.4918		
24	HAL	RESPHOST	LVCF	0.94621	0.47459	1.8865	0.87519	84	48	57.1429	94	59	62.7660		
25	HAL	RESPJMCK	OBSERVED CASES	0.97707	0.58892	1.6211	0.92845	135	78	57.7778	163	102	62.5767		
26	HAL	RESPJMCK	LVCF	0.84429	0.56630	1.2587	0.40617	193	84	43.5233	264	117	44.3182		
27	HAL	RESPMOOD	OBSERVED CASES	1.07406	0.64692	1.7832	0.78238	122	59	48.3607	151	82	54.3046		
28	HAL	RESPMOOD	LVCF	0.85891	0.57051	1.2931	0.46624	174	70	40.2299	262	104	39.6947		
29	CHL	RESPANX	OBSERVED CASES	0.85243	0.45192	1.6079	0.62191	79	47	59.4937	86	49	56.9767		
30	CHL	RESPANX	LVCF	0.97007	0.56382	1.6690	0.91260	97	49	50.5155	120	60	50.0000		
31	CHL	RESPBPRS	OBSERVED CASES	1.03509	0.56713	1.8892	0.91054	90	48	53.3333	109	62	56.8807		
32	CHL	RESPBPRS	LVCF	0.91834	0.54623	1.5439	0.74791	108	51	47.2222	148	70	47.2973		
33	CHL	RESPFI	OBSERVED CASES	0.82522	0.39631	1.7183	0.60770	66	47	71.2121	70	47	67.1429		
34	CHL	RESPFI	LVCF	0.83306	0.45998	1.5087	0.54668	83	49	59.0361	98	53	54.0816		
35	CHL	RESPFV	OBSERVED CASES	1.78671	0.93059	3.4304	0.08119	78	44	56.4103	100	72	72.0000		
36	CHL	RESPFV	LVCF	1.43833	0.84486	2.4487	0.18057	97	46	47.4227	142	83	58.4507		
37	CHL	RESPHOST	OBSERVED CASES	1.24363	0.48324	3.2005	0.65120	43	31	72.0930	56	42	75.0000		
38	CHL	RESPHOST	LVCF	1.15565	0.55359	2.4125	0.70006	52	33	63.4615	85	55	64.7059		

39	CHL	RESPJMCK	OBSERVED CASES	1.65117	0.86943	3.1358	0.12542	85	49	57.6471	99	70	70.7071		
40	CHL	RESPJMCK	LVCF	1.34230	0.79542	2.2652	0.27018	102	50	49.0196	141	81	57.4468		
41	CHL	RESPMOOD	OBSERVED CASES	0.86268	0.42215	1.7629	0.68541	69	48	69.5652	81	55	67.9012		
42	CHL	RESPMOOD	LVCF	1.15954	0.65175	2.0630	0.61456	88	49	55.6818	112	66	58.9286		
43	RIS	RESPANX	OBSERVED CASES	3.88134	1.37216	10.9789	0.01058	24	10	41.6667	64	45	70.3125	*	
44	RIS	RESPANX	LVCF	2.13994	0.88505	5.1741	0.09123	30	11	36.6667	94	50	53.1915		
45	RIS	RESPBPRS	OBSERVED CASES	7.78886	3.18149	19.0685	0.00001	33	11	33.3333	87	69	79.3103	*	
46	RIS	RESPBPRS	LVCF	5.11447	2.28449	11.4501	0.00007	38	11	28.9474	111	75	67.5676	*	
47	RIS	RESPFI	OBSERVED CASES	3.06761	1.21658	7.7349	0.01753	29	13	44.8276	60	43	71.6667	*	
48	RIS	RESPFI	LVCF	2.07549	0.91839	4.6904	0.07920	33	14	42.4242	90	55	61.1111		
49	RIS	RESPFV	OBSERVED CASES	7.49615	2.78970	20.1428	0.00006	29	14	48.2759	82	72	87.8049	*	
50	RIS	RESPFV	LVCF	3.27074	1.46442	7.3051	0.00385	33	14	42.4242	113	80	70.7965	*	
51	RIS	RESPHOST	OBSERVED CASES	0.85487	0.08322	8.7819	0.89504	6	5	83.3333	32	26	81.2500		
52	RIS	RESPHOST	LVCF	0.45404	0.04884	4.2213	0.48764	7	6	85.7143	41	30	73.1707		
53	RIS	RESPJMCK	OBSERVED CASES	8.23135	3.24559	20.8761	0.00001	33	14	42.4242	85	73	85.8824	*	
54	RIS	RESPJMCK	LVCF	4.16116	1.91339	9.0495	0.00032	38	14	36.8421	113	80	70.7965	*	
55	RIS	RESPMOOD	OBSERVED CASES	3.01674	1.19839	7.5941	0.01907	28	13	46.4286	72	53	73.6111	*	
56	RIS	RESPMOOD	LVCF	1.90436	0.85426	4.2453	0.11529	33	14	42.4242	104	62	59.6154		

OBS	COMP	END	ANAL	EST	LCL	UCL	P	SERN	SERR	SER%	COMPN	COMPR	COMP%	SIG
1	PLA	RESPANX	OBSERVED CASES	1.07810	0.71502	1.62556	0.71964	201	105	52.2388	217	127	58.5253	
2	PLA	RESPANX	LVCF	0.94935	0.67727	1.33075	0.76292	276	117	42.3913	349	159	45.5587	
3	PLA	RESPBPRS	OBSERVED CASES	1.04969	0.71774	1.53517	0.80255	229	118	51.5284	273	158	57.8755	
4	PLA	RESPBPRS	LVCF	0.95217	0.69252	1.30918	0.76289	304	123	40.4605	410	177	43.1707	
5	PLA	RESPFI	OBSERVED CASES	0.94098	0.61739	1.43419	0.77725	183	108	59.0164	221	130	58.8235	
6	PLA	RESPFI	LVCF	0.82950	0.59196	1.16237	0.27751	252	121	48.0159	358	159	44.4134	
7	PLA	RESPFV	OBSERVED CASES	1.40105	0.93230	2.10550	0.10466	210	124	59.0476	268	190	70.8955	
8	PLA	RESPFV	LVCF	1.28047	0.93198	1.75928	0.12717	291	135	46.3918	404	228	56.4356	
9	PLA	RESPHOST	OBSERVED CASES	1.03770	0.53400	2.01653	0.91305	95	65	68.4211	117	85	72.6496	
10	PLA	RESPHOST	LVCF	1.04078	0.62963	1.72042	0.87614	136	81	59.5588	179	114	63.6872	
11	PLA	RESPJMCK	OBSERVED CASES	1.20292	0.81050	1.78536	0.35910	220	127	57.7273	262	172	65.6489	
12	PLA	RESPJMCK	LVCF	0.99858	0.72775	1.37018	0.99297	295	134	45.4237	405	198	48.8889	
13	PLA	RESPMOOD	OBSERVED CASES	1.00575	0.66620	1.51835	0.97823	191	107	56.0209	232	137	59.0517	
14	PLA	RESPMOOD	LVCF	0.94434	0.67704	1.31716	0.73585	262	119	45.4198	374	170	45.4545	

Technical Document (TD004)

Approved for issue by:

Andrew Gorman
Project Team Physician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

Emma Westhead
Senior Statistician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

EXHIBIT 20

1) angioedema
2) ~~Lmited~~
3) hyperglyc, diabetes

DISCUSSION DOCUMENT

US - involuntary movements
CDS - discussion

SEROQUEL™

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

ALL FINDINGS PRESENTED IN THIS DOCUMENT ARE TO BE SUBJECT TO FURTHER CONSIDERATION AT SERM

6 cases
median time to onset new diabetes 0.5 mos.

Wayne
PB 2240
base rates

gov't

Emma, MJ - dose response
Geoff - 6 cases, conclusions

Lumy CDS in line w US PT's

CONCLUSION: KEEP ISSUE UNDER REVIEW

AUTHOR(S):

Wayne K. Geller MD
Medical Director, Drug Safety
Wilmington, DE

SIGNATURE: .....

DATE: .....

of 10 cases from clinical trials → each source?

 RIS labelled for diabetes, DKA

SUMMARY AND CONCLUSIONS:

Presently, the SEROQUEL Core Data Sheet (CDS) does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with SEROQUEL therapy. Safety data derived from clinical trials and spontaneous reports, despite often containing limited information, suggest the possibility of an association between SEROQUEL use and impaired glucose regulation including occasional reports of new onset diabetes mellitus. While none of these reports are absolutely steadfast, the number of reports is fairly sizeable. Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis. While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

1 INTRODUCTION

criteria used in this assessment: FBS 7126, 2hr post 75gm 7200

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for SEROQUEL and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for SEROQUEL for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The SEROQUEL core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with SEROQUEL:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The SEROQUEL US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels $\geq$110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

(1) Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or

(2) Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or

(3) Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with
Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:

Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)

- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12 to 16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

(1) The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).

(2) Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Frequent (>10%): Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

16 spont
no attributes ← 10 clin trials
2 lit reports

Clozapine: *Warnings and Precautions*:

Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.

Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases.

9 cases new onset

Case Number: 2000UW01164

4 DKA, 2 new onset
2 unsure

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

NKHOC - 0

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started SEROQUEL 200 mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on SEROQUEL. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving SEROQUEL, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving SEROQUEL 300 mg daily since 06 December 1999. On 26 January 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. SEROQUEL was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include zoloft, klonopin, haldol and depakote.

Follow-up 23 February 2000: Pharm D reports that "after further testing, the attending physicians did not feel that SEROQUEL was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving SEROQUEL and developed diabetes. Physician feels that SEROQUEL may possibly be responsible for the development of diabetes.

Follow-up 11 November 1999: Physician reports that the 47 year old female (not 45) had been receiving SEROQUEL 600 mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. SEROQUEL was tapered for discontinuation. Concomitant medications include klonopin and benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "SEROQUEL caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS

A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving SEROQUEL 100 mg every evening since January 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of SEROQUEL was decreased to 50 mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 September 1999, SEROQUEL dosage was again decreased to 25 mg every evening. The patient had been receiving risperidol prior to

SEROQUEL. Concomitant medications include ritalin for attention disorder and serzone for depression.

Case Number: 1999UW00969

COMPLICATIONS OF DIABETES MELLITUS

A report has been received from a physician concerning a 28 year old male patient who was taking SEROQUEL and lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14 March 1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.

*Follow-up received 22 March 1999: A pharmacist reports that the patient started zithromax on 10 March 1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14 March 1999: The patient presented on 14 March 1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15 March 1999. The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05 May 1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10 to 16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967

DIABETES

A report has been received from a physician concerning a 17 year old male who is receiving SEROQUEL 200 mg twice daily for schizophrenia. The patient was initially started on 100 mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300 mg daily. Patient also receives paxil and depakote. Patient continues on SEROQUEL.

Case Number: 1999UW00288

BLOOD SUGAR RISING

A report has been received from a 58-year-old diabetic female patient who has been receiving SEROQUEL since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 January 1999 the reading was 321.

Case Number: 1999AP06660

LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA

A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving SEROQUEL since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300 to 400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started SEROQUEL in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control, particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5 mg/day. At the time of reporting the events were ongoing.

The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757

DIABETES, KETOACIDOSIS.

A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750 mg daily for psychosis since November 1997. He was receiving acamprosate, depixol and priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.

The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218

DIABETES DURING PREGNANCY

Patient developed diabetes during pregnancy and started insulin on 30 September 1999. Baby due 06 December 1999, but patient's water broke 30 September 1999 and baby born in October 1999. See case 1999AP06076.

Case Number: 1999AP02989

DIABETES MELLITUS

This patient started treatment with SEROQUEL on 13 November 1998 and with fluoxetine on 12 November 1998. Urine and blood tests on 26 November 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985

NON INSULIN DEPENDENT DIABETES

A physician reported that a 44 year male patient was given SEROQUEL 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting SEROQUEL, the patient developed non-insulin dependent diabetes. SEROQUEL was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554

CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.

A report has been received from a physician concerning a 58 year old male patient who received SEROQUEL 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081

HYPERGLYCAEMIA

Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 1998. Open label medication started on 14 September 1998 and ended on 26 September 1998. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844

HYPERGLYCAEMIA, DIABETES.

A report has been received from a physician concerning a male patient in his early forties who has been receiving SEROQUEL for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.

NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken SEROQUEL since July 1998. On 31 August 1998 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 October 1999: Further information reveals that the patient was receiving SEROQUEL 200 mg for a bipolar disorder since July 1998. On 31 August 1999, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. SEROQUEL was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408

HYPERGLYCAEMIA (NON-SERIOUS)

A pharmacist and a nurse reported that a male patient taking SEROQUEL developed hyperlycaemia. The pharmacist considered the event unrelated to SEROQUEL; the nurse considered the event related to SEROQUEL. The patient was also taking stelazine.

Case Number: 1998AP45979

LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR

Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with SEROQUEL, SEROQUEL dosage has been reduced from 400 to 200mg. The physician is thinking of stopping SEROQUEL altogether.

Case Number: 1998AP18089

HYPERGLYCAEMIA.

A report has been received from a physician concerning a 32 year old male patient who has been receiving SEROQUEL from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.

On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803

DIABETIC KETOACIDOSIS

A report has been received from a physician concerning a 36 year old male who has been receiving SEROQUEL in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. SEROQUEL started on 06 September 1996. The patient had recently been diagnosed with diabetes mellitus which was controlled on glucotrol. On 18 March 1997, 28 weeks after starting SEROQUEL, he was admitted to hospital with decreased level of consciousness. He had not been taking his glucotrol or SEROQUEL for 3 to 4 days prior to admission. He was given IV fluids and insulin but later developed severe acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were:

sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin and food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted SEROQUEL. The event resolved on 01 April 1997. The investigator felt that there was not a reasonable possibility that the event was related to SEROQUEL.

Case Number: 1997AP36246

UNCONTROLLED DIABETES

A report has been received from a physician concerning a 29-year old male who has been receiving SEROQUEL since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. SEROQUEL treatment was put on hold and the patients diabetes treated with humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the SEROQUEL therapy.

Case number: 1997AP35710

UNCONTROLLED DIABETES MELLITUS

A report has been received regarding a 45 year old male who has been receiving SEROQUEL as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 August 1997, 163 days after starting SEROQUEL, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.

The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874

PNEUMONIA, DIABETES, HYPERTENSION

This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with SEROQUEL as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.

The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737

DIABETES MELLITUS

This 52 year-old-female with schizophrenia was taking SEROQUEL 400 mg from 28 January 1995 as part of a clinical trial. On 31 January 1995 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April 1995, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.

This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544

AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in SEROQUEL trial on 26 September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4 November, the patient developed

symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with SEROQUEL.

Case Number: 1994AP03286

HYPERGLYCAEMIA

An investigator reported that a 53 year old female patient started taking SEROQUEL on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893

HYPERGLYCAEMIA

An investigator reported that a 45 year old male was treated with SEROQUEL beginning on 4 March 1994. Concomitant medications included zantac and haldol. The patient had no history of diabetes mellitus. He had recently stopped taking an unblinded SEROQUEL study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. SEROQUEL was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5 DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of pre-existing diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of pre-existing diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to SEROQUEL.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily SEROQUEL dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months

(median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily SEROQUEL dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to 21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking SEROQUEL 150 mg daily for 30 months. The latter report contains scant information, except the daily SEROQUEL dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient

Note Wayne impressed by 2 physicians noting ~~dose~~ diabetes onset with dose increase.

developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, consideration should be given to the suggestion that SEROQUEL therapy may cause impaired glucose regulation including diabetes mellitus in certain individuals.

6 REFERENCES

(1) Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

(2) American Diabetes Association: Clinical Practice Recommendations 2000, Volume 23 Supplement 1, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

(3) Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

(4) Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

Usually no baseline fasting glucose
7 had taking decrep assoc w diabetes
Some reports - scant info
No + de or re challenge

Seroquel may cause impaired glucose regulation in some individuals.
No ~~of~~ signal of Type 1 ie no negative impact on insulin production

DISCUSSION
No + re, de challenge
No bsl CHO
low # of cases for a common condition
No mechanism of effect

For my part of 4 cases, DKA speaks to absence of dechallenge effect.

other pts
1. will get long term data from okay trial
2. will know more after response to FDA concludes

EXHIBIT 21

ACCESSION NUMBER:

SAFETY POSITION PAPER

'SEROQUEL'

DIABETES MELLITUS, DIABETIC KETOACIDOSIS, NON-KETOTIC HYPEROSMOLAR COMA, AND HYPERGLYCAEMIA

AUTHOR:
Wayne K. Geller, MD
Global Drug Safety Physician
Wilmington, DE

SIGNATURE: .....

DATE: .....

SUMMARY AND CONCLUSIONS:

Currently, the Seroquel CDS does not include any references to diabetes mellitus, diabetic ketoacidosis, or hyperglycaemia associated with Seroquel therapy. Safety data derived from clinical trials and spontaneous reports often containing limited information may represent a weak signal linking Seroquel with impaired glucose regulation, including occasional reports of new onset diabetes mellitus. None of these reports are absolutely steadfast (i.e., there are no clear index cases and there were no reports of positive dechallenges/rechallenges) and most have either incomplete information or other explainable causes. Although the number of reports is fairly sizable, it was felt that there is insufficient evidence at present to warrant an amendment to the Seroquel CDS. However, it was agreed that this topic will be kept under ongoing review and will be reassessed at a later time. Additional clinical trials are planned in which baseline fasting blood glucose concentrations will be obtained as well as follow-up measurements on study drug.
Currently, no such signals exist for the complications of diabetes such as non-ketotic hyperosmolar coma or diabetic ketoacidosis.

1 INTRODUCTION

In May 2000 FDA notified AstraZeneca that, based upon review of postmarketing safety data for Seroquel and other atypical antipsychotics, they were further investigating a possible signal for new onset diabetes mellitus (NODM), non-ketotic hyperosmolar coma (NKHOC), and diabetic ketoacidosis (DKA). FDA expressed concern that increased market exposure could result in an increased number of reports of these events as has been observed with similar agents. In there correspondence (see attachment), they have requested "more extensive safety information" from all phases of clinical development to the present for Seroquel for their review. This discussion document will specifically address FDA's third item on their list of requests, "A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperglycaemia, hyperosmolar coma, diabetic ketoacidosis, and weight gain".

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[1], several of these products have in their labels statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:

Hyperglycaemia:

Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycaemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL® (clozapine) should be considered.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

2 BACKGROUND

The Seroquel core data sheet (CDS) last revised in March 2000 does not include listings for NODM, hyperglycaemia, NKHOC, or DKA. The following statement addresses the issue of weight gain with Seroquel:

"As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

The Seroquel US package insert (PI) includes hyperglycaemia and diabetes mellitus as labeled events occurring infrequently (in 1/100 to 1/1000 patients) according to premarketing clinical trial safety data. The aforementioned complications of diabetes mellitus are not in the PI.

Patients with either impaired glucose tolerance (IGT) or frank diabetes mellitus have hyperglycaemia [2]. The term IGT represents a metabolic condition between normal glucose homeostasis and diabetes mellitus. This includes individuals with fasting glucose levels ≥110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l).

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The criteria for the diagnosis of DM are as follows:

1. Symptoms of DM (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l); or
2. Minimum 8 hour fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l); or
3. Two hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using a glucose equivalent of 75 g anhydrous glucose dissolved in water

Patients with diabetes mellitus are classified as having Type I or Type 2 disease. Patients with Type 1 disease are absolute insulin deficient with β-cell destruction and are at risk for developing DKA. Patients who develop Type 2 disease have both abnormal insulin secretion and insulin resistance in target tissues and are not at risk for developing DKA. It is felt that insulin resistance in these patients is the primary event and that obesity contributes to insulin resistance [3]. Type 2 diabetes mellitus is most prevalent and is thought to be a polygenic disease. The majority of patients with Type 2 disease are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2), but this is not thought to be the only factor that contributes to insulin resistance. Individuals with dyslipidemia and/or hypertension are at increased risk. There is a strong genetic predisposition to Type 2 disease. It is well known that a modest weight reduction in an obese individual with Type 2 DM frequently results in significant reduction in blood glucose levels. This is the cornerstone of therapy in patients with Type 2 diabetes mellitus, prior to and during treatment with pharmacologic agents.

Diseases and conditions that have been associated with diabetes mellitus include pancreatic diseases, acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, congenital rubella, cytomegalovirus, pregnancy, and others. Drugs that are known to cause or contribute to hyperglycaemia include: pentamidine, nicotinic acid, glucocorticoids, thyroxine, diazoxide, β-agonists, thiazide diuretics, phenytoin, α-interferon, and others.

Criteria for testing for DM in otherwise asymptomatic, undiagnosed individuals are as follows:
Individuals ≥ 45 years of age, or younger in patients who:

- Are obese (≥ 120% desirable body weight or a BMI ≥ 27 kg/m^2)
- Have a first degree relative with DM
- Belong to high-risk population
- Delivered a ≥ 9 pound baby or have been diagnosed with gestational DM
- Are hypertensive (≥140/90 mmHg)
- Have hyperlipidemia
- Have had abnormal IGT or IFG

3 THE LITERATURE

Wilson et al [4] presented a poster entitled, *New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics* at the American College of Neuropsychopharmacology Annual Meeting, December 12-16, 1999, in Acapulco, Mexico. They evaluated the risk of patients using atypical antipsychotics for developing new-onset diabetes mellitus and ketoacidosis. Their interest evolved from case reports in the literature describing altered glucose metabolism in patients receiving atypical antipsychotic agents (notably clozapine, olanzapine, and quetiapine). They conducted a retrospective analysis of the Ohio Department of Mental Health database searching for patients treated with an atypical antipsychotic agent who had also been evaluated or treated for diabetes mellitus. In 11 of 126 (8.7%) of patients receiving clozapine, olanzapine, or quetiapine were diagnosed with new-onset, acute, or market glucose intolerance. Six of these patients required insulin (4 short-term) and five developed DKA. Confounding these results are that only 21/126 patients studied had baseline fasting glucose and that only 14 patients had follow-up studies. Their findings were that:

1. The mean and median time to onset of diabetic ketoacidosis after starting treatment with atypical antipsychotic medications were 81 and 33 days, respectively (N=5).
2. Changes in glucose tolerance were not related to significant weight gain and often occurred during the first 6 weeks of treatment. Mean and median weight gains in patients with new-onset DM were 16 and 8 pounds, respectively.

Reviewing the labeling for other atypical antipsychotic medications (risperidone, olanzapine, clozapine, and sertindole)[4], several of these products have in their label statements regarding diabetes mellitus, diabetic ketoacidosis, and/or severe hyperglycaemia.

Risperidone: No mention of diabetes or hyperglycaemia.

Olanzapine: Warnings and Precautions: Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during Zyprexa treatment. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
Frequent (>10%):
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also section 4.4, 'Special warnings and special precautions for use').

Clozapine: *Warnings and Precautions*:
Undesirable effects: On rare occasions, hyperglycaemia has been reported in patients on Clozaril treatment.

Sertindole: Warnings and Precautions: *Diabetic patients:* Serdolect may modify insulin and glucose responses in diabetic patients calling for adjustment of antidiabetic therapy.
Side-effects: Convulsions, hyperglycaemia and syncope have been reported rarely.

4 CLINTRACE DATABASE (IN HOUSE SAFETY DATA)

A search was conducted for all cases in which diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with Seroquel. The following are narratives for these 28 cases.

Case Number: 2000UW01164

KETOACIDOSIS, DIABETES MELLITUS, POLYURIA, POLYDIPSIA, WEIGHT LOSS, ELEVATED GLUCOSE LEVEL

A report has been received from a registered pharmacist, via sales rep, concerning a 43 year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

Case Number: 2000UW01047

COUGH, ELEVATED CHOLESTEROL, WEIGHT GAIN, CONSTIPATION, ASTHMA, WORSENING FIBROMYALGIA, MUSCLE SPASMS, TENSENESS IN NECK, URINE ODOR, WORSENING ARTHRITIS, WORSENING ENDOMETRIOSIS, ELEVATED BLOOD SUGAR, EXCITABLE, DIFFICULTY IN WAKING, NEGATIVE MOOD, DECREASED SEX DRIVE, INABILITY TO HAVE ORGASMS

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

Case Number: 2000UW00266

DIABETES MELLITUS

A report has been received from a pharmacist concerning a 12 year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycaemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170. Concomitant medications include Zoloft, Klonopin, Haldol and Depakote. Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycaemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

Case Number: 1999UW03532

DIABETES MELLITUS, WEIGHT GAIN

A report has been received from a physician concerning a 45 year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes. Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues, it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

Case Number: 1999UW03387

TYPE II DIABETES, DROWSINESS
A report has been received from a physician concerning a 17 year old Hispanic male patient who had been receiving Seroquel 100mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime, the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

Case Number: 1999UW00969
COMPLICATIONS OF DIABETES MELLITUS
A report has been received from a physician concerning a 28 year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of an increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240, potassium low, CPK normal, Lithium level was not elevated (0.4 or 0.6). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on 14-Mar-1999. The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending.
*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.
*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no doll's eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli. Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on 15-Mar-1999. The reporter attributed the event to a drug effect from multiple prescriptions.
*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 10-16 lb weight loss with flu-like symptoms, and blood glucose of 2240 on admission.

Case Number: 1999UW00967
DIABETES
A report has been received from a physician concerning a 17 year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with Glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Case Number: 1999UW00288
BLOOD SUGAR RISING
A report has been received from a 58-year-old diabetic female patient who has been receiving Seroquel since September 1997. In 1994 she was diagnosed with diabetes mellitus. In 1997 her blood sugar readings began rising and on 20 Jan 99 the reading was 321.

Case Number: 1999AP06660
LOSS OF DIABETIC CONTROL, TOOTH PAIN, INSOMNIA
A report has been received from a pharmacist concerning a 45 year old male patient who has been receiving Seroquel since April 1999 for treatment of schizophrenia. The patient began quetiapine therapy on 300-400 mg/day and increased to 750 mg/day in September/October 1999. For two years previously, the patient had a history non-insulin dependent diabetes mellitus. This was initially treated with metformin and then diet-controlled only until he started Seroquel in April 1999. After staring quetiapine therapy, the patient developed a loss of diabetic control,

particularly on the higher dosage. Blood glucose which was previously stable at 10 (units unknown) rose to 13 or greater. He was treated with glibenclamide 7.5mg/day. At the time of reporting the events were ongoing.
The reporter felt that the loss of diabetic control was related to quetiapine therapy due to the temporal relationship. It was noted that the patient had a history of non-insulin dependent diabetes mellitus that was previously diet controlled.

Case Number: 1999AP05757
DIABETES, KETOACIDOSIS.
A report has been received from a physician concerning a 25 year old male patient who has been receiving quetiapine fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly. In August 1999, 1 year 9 months after starting quetiapine fumarate, the patient was hospitalised due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and quetiapine is continuing.
The reporter had no opinion regarding the causal relationship between the events and quetiapine fumarate, but commented that the weight gain may have been a contributing factor.

Case Number: 1999AP05218
DIABETES DURING PREGNANCY
Patient developed diabetes during pregnancy and started insulin on 30 Sept 99. Baby due 06 December 1999, but patient's water broke 30 Sept 99 and baby born in Oct 99. See case 1999AP06076.

Case Number: 1999AP02989
DIABETES MELLITUS
This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 17.1.

Case Number: 1999AP01985
NON INSULIN DEPENDENT DIABETES
A physician reported that a 44 year male patient was given Seroquel 250 mg BID for resistant schizophrenia. Treatment began on 27 August 1998. Concomitant medication included clonazepam, sodium valproate and cyproterone. The patient had no history of diabetes mellitus and was being treated with cyproterone for a disorder of sexual inhibition. Five months after starting Seroquel, the patient developed non-insulin dependent diabetes. Seroquel was stopped toward the end of January 1999. No follow-up is available.

Case Number: 1998UW49554
CEREBROVASCULAR ACCIDENT, DIABETIC ACIDOSIS, TRANSIENT ISCHEMIC ATTACK, COLLAPSE.
A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

Case Number: 1998UW49081
HYPERGLYCAEMIA
Patient is an 83 year old female who was admitted to the hospital on 27 September 1998 with a diagnosis of hyperglycaemia. Past history and medical conditions include diabetes mellitus. The first patient completed the double-blind portion of the trial on 14 September 98. Open label medication started on 14 September 98 and ended on 26 September 98. This event took place on day 12 of study medication at a dose of 25 mg. In the opinion of the investigator, the elevated blood sugar was not related to the study medication.

Case Number: 1998UW48844
HYPERGLYCAEMIA, DIABETES.
A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for four weeks and is experiencing hyperglycaemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl.
NEW ONSET DIABETES MELLITUS ASSOCIATED WITH THE INITIATION OF QUETIAPINE TREATMENT, J OF CLINICAL PSYCHIATRY, 60: 556-557, AUG 99, USA, SOBEL, M., JAGGERS, ED, FRANZ, MA

Case Number: 1998UW48512
DIABETES MELLITUS
A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.
*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 99, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycaemia. Four months prior to admission blood glucose was 126 mg/dL and 107 mg/dL. At admission blood glucose was 607 mg/dL. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.
SOBEL M, JAGGERS ED, FRANZ MA: NEW-ONSET DIABETES MELLITUS... J OF CLIN PSYCHIATRY; 1999;60(8):556-557.

Case Number: 1998AP50408
HYPERGLYCAEMIA (NON-SERIOUS)
A pharmacist and a nurse reported that a male patient taking Seroquel developed hyperlycaemia. The pharmacist considered the event unrelated to Seroquel; the nurse considered the event related to Seroquel. The patient was also taking Stelazine.

Case Number: 1998AP45979
LOSS OF DIABETIC CONTROL, AGGRESSIVE BEHAVIOUR, STROPPY BEHAVIOUR
Patient had actually been messing about with his insulin injections that weekend, the event therefore had nothing to do with Seroquel, Seroquel dosage has been reduced from 400 to 200mg. The physician is thinking of stopping Seroquel altogether.

Case Number: 1998AP18089
HYPERGLYCAEMIA.
A report has been received from a physician concerning a 32 year old male patient who has been receiving Seroquel from 21 May 1995 for psychosis as part of a clinical trial. The patient has a medical history of obesity, abdominal pain, indigestion, constipation, muscle stiffness, restlessness, depression, and hypertension. He was also taking valproate semisodium, benztropine mesylate and propranolol.
On 26 January 1998, 2 years 36 weeks after starting study medication, the patient was found to have hyperglycaemia and was hospitalised. At the time this report was received, the event was still ongoing. The study drug was stopped on 01 February 1998 due to the potential effect of unstable glucose levels on the patient's mood. The reporter considered that there was not a reasonable possibility that this event was related to the study therapy.

Case Number: 1997AP36803
DIABETIC KETOACIDOSIS
A report has been received from a physician concerning a 36 year old male who has been receiving Seroquel in a dose up to 500 mg daily for schizophrenia as part of a clinical trial. Seroquel started on 06 Sept 96. The patient had recently been diagnosed with diabetes mellitus which was controlled on Glucotrol. On 18 March 97, 28 weeks after starting Seroquel, he was admitted to hospital with decreased level of consciousness. He had not been taking his Glucotrol or Seroquel for 3-4 days prior to admission. He was given IV fluids and insulin but later developed severe

acidosis and an increased lipase of 1819 u/l(25-229)and amylase of 135u/l(27-92). Other abnormal laboratory findings were: sodium 130 mmol/l (135-146), chloride 99 mmol/l (100-107), bicarbonate 5mmol/l (22-32), creatinine 1.9 mg/dl (0.4-1.4), glucose 413mg/dl (70-160), uric acid 12.3mg/dl (2.2-7.2), White blood count 17,000 (4,000-11000), beta-hydroxy butyrate 182mg/dl(0.4-4). The patient was started on subcutaneous insulin & food was started once amylase and lipase were within normal range. At the time of reporting the patient had not restarted Seroquel. The event resolved on 01 April 97. The investigator felt that there was not a reasonable possibility that the event was related to Seroquel.

Case Number: 1997AP36246
UNCONTROLLED DIABETES
A report has been received from a physician concerning a 29-year old male who has been receiving Seroquel since 22 January 1997 in a clinical trial for schizophrenia. After 8 months treatment, the patient was attending a hospital trial visit on 23 September 1997 when he felt faint and collapsed. He was found to have elevated blood glucose, decreased blood pressure (70/50) and an abnormal ECG with cardiac enzymes raised. Seroquel treatment was put on hold and the patients diabetes treated with Humulin in Hospital. The event was ongoing at the time of the report. The physician felt that there was not a reasonable possibility that this event was related to the Seroquel therapy.

Case number: 1997AP35710
UNCONTROLLED DIABETES MELLITUS
A report has been received regarding a 45 year old male who has been receiving Seroquel as part of a clinical trial. He has a medical history of diabetes mellitus, insomnia, gonorrhoea, genital herpes, alcohol and heroin abuse. His concomitant medications were clonazepam, amitriptyline, famotidine and lisinopril. On 10 Aug 97, 163 days after starting Seroquel, he had a moderately severe episode of uncontrolled diabetes mellitus requiring hospital treatment. He recovered after IV fluids and a 2200 calorie diabetic diet. He remains in the trial.
The investigator considered the event not related to trial therapy.

Case Number: 1996AP19874
PNEUMONIA, DIABETES, HYPERTENSION
This 65-year old male patient with Parkinsons disease, anaemia of chronic disease, obsessive compulsive disorder, penile implant, and peptic ulcer disease was being treated with Seroquel as part of a clinical trial. The patient was receiving gastric tube nutrition secondary to poor gag reflex. Treatment began on 21 September 1995. Earlier in the year the patient had been hospitalised suffering from pneumonia. On 28 March 1995, the patient complained of chest congestion. X-ray confirmed that he had pneumonia. He was treated with antibiotic in his nursing home but was later admitted to hospital for further antibiotic treatment. During his admission, he was noted to have elevated blood sugar and blood pressure. Discharge diagnoses were right lower lobe pneumonia, possible nasotracheal aspiration, new onset diabetes and hypertension. The diabetes and hypertension were considered to be not regulatory serious and not related to trial therapy.
The investigator considered the pneumonia was not related to trial therapy.

Case Number: 1995AP10737
DIABETES MELLITUS
This 52 year-old-female with schizophrenia was taking Seroquel 400 mg from 28 January 95 as part of a clinical trial. On 31 January 95 this patient was hospitalised with diabetes mellitus. She was not withdrawn from the trial. When first reported 3rd April '95, this event was considered probably not related. However, further information now reveals that elevated sugar levels have been detected in this patient for two years. Therefore it is considered that her diabetes was definitely not related to the study medication.
This event is now regarded as non-serious by the investigator as it was symptoms of the patient's schizophrenia which led to prolonged hospitalisation and not the diabetes.

Case Number: 1994AP04544
AGITATION, UNREST, INCOMMUNICATIVE, DISINHIBITION, PARANOIA, DIABETES, INCREASED TRIGLYCERIDES

Patient with impaired glucose metabolism pre-trial. Entered in Seroquel trial on 26th September. On study day 8 this patient developed an acute psychosis, suggesting lack of efficacy, which led to withdrawal from the trial. On 4th November, the patient developed symptoms of diabetes. Physician assessment is that there is no reason to suspect that development of diabetes is related to treatment with Seroquel.

Case Number: 1994AP03286
HYPERGLYCAEMIA
An investigator reported that a 53 year old female patient started taking Seroquel on 22 July 1994. The patient had a history of insulin-treated diabetes and had been taking several concomitant medications. On 8 August 1994, the patient was noted to be hyperglycaemic. The investigator reported that the patient had the same level of hyperglycaemia that she had prior to study entry.

Case Number: 1994AP00893
HYPERGLYCAEMIA
An investigator reported that a 45 year old male was treated with Seroquel beginning on 4 March 1994. Concomitant medications included Zantac and Haldol. The patient had no history of diabetes mellitus. He had recently stopped taking a n unblinded Seroquel study drug. On 3 March, the fasting blood sugar was 393. The following day, it rose slightly before increasing to 1104 on 13 March. Seroquel was stopped that day. No treatment was reported but the blood glucose on 14 March was 200.

5 DISCUSSION

There were 27 reports of diabetes mellitus and 2 reports of hyperglycaemia received by AstraZeneca to date. New onset diabetes mellitus was described in 19 of these 27 reports and exacerbation of preexisting diabetes mellitus accounted for 8 reports. Four reports described patients who developed diabetic ketoacidosis (2000UW01164, 1999AP05757, 1998UW49554, and 1997AP36803). Two of these were new onset reports and the other two involved worsening of preexisting diabetes mellitus. There have been no reported cases of non-ketotic hyperosmolar coma received to date. Of these total 28 reports, 16 were spontaneous reports, 10 were from clinical trials, and 2 were literature reports. The investigator attributed none of the cases reported from clinical trials to Seroquel.

New onset diabetes mellitus: There have been 19 cases of new onset diabetes mellitus reported to date. The age range for patients with new onset diabetes mellitus is 12 to 65 with an average age at onset of 37.5 years (median = 41 years). There is a male predominance with males constituting 74% of all reports. Daily Seroquel dosages ranged from 50 mg to 800 mg, with an average daily dose of 419 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 6.2 months with a range of 3 days to 27 months (median = 2.5 months). Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl.

Two patients who developed new onset diabetes mellitus also experienced weight gain (1999UW03532 and 1999AP05757). The latter patient also had diabetic ketoacidosis. One patient who developed hyperglycaemia also experienced weight gain (2000UW01047). Weight gain was not reported in any other cases.

Two patients with new onset diabetes mellitus experienced dose related loss of glycemic control as reported by their physicians (1999UW00969 and 1998UW48512).

Diabetic ketoacidosis: There have been 4 cases of diabetic ketoacidosis reported to date all involving males. The age range for patients with diabetic ketoacidosis is 25 to 58 with an average age at onset of 40.5 years. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 562 mg (median = 625 mg). The average time interval between initial therapy and the date of the reported event was 9.7 months with a range of 1 to

21 months. Two patients with new onset diabetes mellitus also developed diabetic ketoacidosis (2000UW01164 and 1999AP05757). The former patient reportedly lost 30 pounds. Only one case (1997AP36803) reported the blood glucose concentration at clinical presentation, which was 413 mg/dl. One patient died of complications of diabetes mellitus (1998UW49554). A second patient (1997AP36803) recently diagnosed with diabetes mellitus, discontinued taking his oral hypoglycemic agent three days before being hospitalized with DKA. A third patient (1999AP05757) with new onset diabetes mellitus also experienced weight gain (unspecified) and at last word required insulin therapy.

Non-ketotic hyperosmolar coma: There have been no reported cases of non-ketotic hyperosmolar coma.

Hyperglycaemia: There have been two reports of hyperglycaemia reported to date (2000UW01047 and 1998AP50408). Blood glucose concentrations were not provided for either patient. The former report involved a 47-year-old female who developed weight gain and hyperglycaemia after taking Seroquel 150 mg daily for 30 months. The latter report contains scant information, except the daily Seroquel dose which was 750 mg.

Confounding factors: Few, if any, of these patients had baseline fasting glucose levels. Seven patients with new onset diabetes mellitus were using concomitant medications known to impair glucose tolerance and cause diabetes mellitus including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, 1999UW00969, and 1998AP18089). This last patient was also reportedly obese. One patient developed Type 1 diabetes mellitus (2000UW00266). Several reports contained only scant information which precluded detailed analysis of these cases.

While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can cause impaired glucose regulation including diabetes mellitus in certain individuals. Consideration should be given to adding diabetes mellitus to the core data sheet based upon postmarketing and clinical trial safety data.

6 REFERENCES

[1] Electronic Medicines Compendium: http://emc.vhn.net: accessed June 5, 2000.

[2] American Diabetes Association: Clinical Practice Recommendations 2000, Volume 23 Supplement 1, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

[3] Foster D. Diabetes mellitus. In: Fauci AS et al, editors. Harrison's Principles of Internal Medicine, 14th Edition. Philadelphia: McGraw-Hill, 1998: 2060-80

[4] Wilson DR, D'Souza L, Sarkar N, Newton M. New-onset diabetes and ketoacidosis with atypical antipsychotics, American College of Neuropsychopharmacology, 1999

EXHIBIT 22

Unknown

From: Wayne Geller
Sent: Monday, September 18, 2000 6:27 PM
To: G=Dorothee; G=Liz
Cc: G=Safety; G=Joy; G=Vikram
Subject: Re: FW: Quetiapine and glucose metabolism disorders

Attachments: SeroquelSERMDMDKAPositionPaper.doc

Dear Liz and Dorothee,

Attached is a position paper based upon my presentation at the last SERM meeting on diabetes mellitus, diabetic ketoacidosis, and non-ketotic hyperosmolar coma. Please feel free to contact me if you have any additional questions.

Thanks and kind regards,
Wayne

SeroquelSERMDMD
KAPositionPaper...

Thanks,
Wayne

To: Wayne Geller/HQ/Astra Merck
cc: /G=Dorothee/S=Wientjes/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL, /G=Safety/S=Mailbox/O=Astra Pharmaceutica BV/P=Astra/A=400NET/C=NL, /G=Joy/I=JA/S=Gulliford/OU=ALDERLEY/O=PHARMS/P=ZENECA/A=TMAILUK/C=GB
From: Liz Smith @ X400
Date: 09/18/2000 11:51 AM GDT
Subject: FW: Quetiapine and glucose metabolism disorders

Message

Dear Wayne
Please find attached below a request from the Dutch regulatory authorities about Seroquel.
I would be grateful if you could reply direct to Dorothee since I am out of the office after tomorrow, and Mary O'Hare is also out of the office this week.
With many thanks and kind regards,
Liz

From: Wientjens, Dorothee (temp. employee)
Sent: 18 September 2000 08:53
To: Smith, Liz EH
Cc: O'Hare, Mary M; Hyde, Margaret EM; Gulliford, Joy JA; Whittaker, Denise D -

R&D
Subject: FW: Quetiapine and glucose metabolism disorders

Dear Mailbox,

Please find enclosed a letter form the Duth authorities concerningQuetialpine and glucose metabolism.
I would be most grateful if you could address his request.

Thank you in advance

Dorothee PWM Wientjens
DSO
AstraZenecaNL

-----Oorspronkelijk bericht-----
Van: Meiners, dhr. drs. A.P. [mailto:ap.meiners@cbg-meb.nl]
Verzonden: dinsdag 5 september 2000 15:35
Aan: Wientjens Dorothee (temp. employee)
Onderwerp: Quetiapine and glucose metabolism disorders

Dear Dorothee,

At a recent pharmacovigilance working party a signal was raised for one of the other atypical antipsychotic drugs in relation to glucose metabolism disorders. Looking at our recent PSUR assessment reports we don-t seem to have recognised this with Seroquel, however, increases in weight and blood lipids are recognised, so it would not seem impossible. A formal request for an overview and assessment report on all reports of glucose metabolism disorders associated with quetiapine use is coming your way as part of conclusions of assessment of a type II variation application currently under review, but to expedite matters I am also already sending you this request by e-mail. Would it be possible to submit such a report on short notice. It probably doesn-t have to be very extensive as it only focusses on a single issue and it could well be that the number of reports is very limited(even if it would require searching your database for terms such as glucose metablism disorder, glucose incresased, hyperglycemia, diabetes, hypoglycemia, etc.)

Sincerely,
==========
Arthur P. Meiners, head of pharmacovigilance
Medicines Evaluation Board
Kalvermarkt 53 PoBox 16229
2500 BE The Hague
Netherlands
tel +31(70)3567492
fax +31(70)3567515
mailto:ap.meiners@cbg-meb.nl

EXHIBIT 23

From: Wientjens, Dorothee (temp. employee)
Sent: Tuesday, October 03, 2000 3:20 PM
To: Geller, Wayne
Subject: RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for yoy fax, which I sent to the local authorities.

Best regards,

Drothee PWM WIentjens
DSO
AstraZenecaNL

-----Oorspronkelijk bericht-----
Van: Geller Wayne
Verzonden: maandag 25 september 2000 22:38
Aan: Wientjens Dorothee (temp. employee); Schotel Luci
Onderwerp: RE: Quetiapine and glucose metabolism disorders

Hi Dorothee,

The document is 11 pages. I can fax a signed copy to you or mail one. If you prefer the latter, please send me your address and I will send it out at once.

Thanks,
Wayne

-----Original Message-----
From: Wientjens, Dorothee (temp. employee)
Sent: Monday, September 25, 2000 5:16 AM
To: Geller, Wayne
Subject: RE: Quetiapine and glucose metabolism disorders

Dear Wayne,

I think it is ok to send me a hard copy by mail. Then I will send it to the authoroties. From tuesday onwards I will be at a conference, so please contact Luci Schotel, our secretary.

Thank you in anticipation.

Dorothee

-----Oorspronkelijk bericht-----
Van: Geller Wayne
Verzonden: vrijdag 22 september 2000 18:25
Aan: Wientjens Dorothee (temp. employee)
Onderwerp: RE: Quetiapine and glucose metabolism disorders
Urgentie: Hoog

Hi Dorothee,

I spoke with our information services department, and it appears that I can not send you a signed PDF-file electronically as you requested. Do you have time for me to send this either as a fax or a signed hard copy?

Please advise. I will not be in the office Monday.

Thanks,

Wayne

-----Original Message-----
From: Wientjens, Dorothee (temp. employee)
Sent: Friday, September 22, 2000 11:51 AM
To: Geller, Wayne
Subject: Quetiapine and glucose metabolism disorders

Dear Wayne,

Thank you for the safety position paper on seroquel. Would you be so kind as to send me the front page of the paper (as a PDF-file) with your signature and date of report, so I can send it to the local authorities.

Thank you in anticipation

Dorothee P.W.M. Wientjens
dso
Astra ZenecaNL

EXHIBIT 26

Id : i.m.42d9083b5f5fe9dd9720b05f6052ad5b
CN : SQ1ED00428632
Date : Tuesday, October 31, 2000 7:20:00 AM GMT
From : Witch, Emma
To : Haas, Edward J
Cc : Geller, Wayne
Subject : RE: Urgent--Request for Seroquel document re Diabetes sent to FDA
Attachments : final document 280800.doc
Custodians : Geller, Wayne

From:
Witch, Emma

Sent:
Tuesday, October 31, 2000 8:25 AM

To:
Haas, Edward J

Cc:
Geller, Wayne

Subject:
RE: Urgent--Request for Seroquel document re Diabetes sent to FDA

Attachments:
final diabetes document 280800

Hi there

CONFIDENTIAL

Here is the diabetes doc that went to the FDA.

Regards

Emma

From: Haas, Edward J

Sent: 30 October 2000 22:50

To: Witch, Emma

Cc: Geller, Wayne

Subject: Urgent--Request for Seroquel document re Diabetes sent to FDA

Hello Emma,

Can you please provide me and Wayne wth a copy of the document that was sent to the FDA regarding diabetes. Thank you very much!

Ed

cid:CHILKAT-CID-469c0a8d-8b33-4364-90d9-a7d90f0ecb84

SEROQUEL™ (quetiapine fumarate)

Response to FDA request for further safety information

To assess the possibility of a causal association between Seroquel treatment and disturbances in glucose regulation

NDA 20-639

August 2000

CONTENTS PAGE

1 INTRODUCTION

The purpose of this document is to provide the FDA with further safety information in order to assess whether there is a causal association between Seroquel treatment and disturbances in glucose regulation, in particular the onset of diabetes.

The FDA have requested 6 pieces of information; these are summarized as follows:

(1) A comprehensive review of all preclinical data pertaining to hyperglycemia.

(2) A thorough assessment of all Phase 1, 2 and 3 studies in the Seroquel NDA for evidence of adverse events possibly related to disturbances in glucose regulation, mean changes from baseline in plasma glucose levels, and the number of patients meeting the criteria for a markedly abnormal plasma glucose concentration.

(3) A review of spontaneous postmarketing reports for new-onset diabetes, hyperosmolar coma, diabetic ketoacidosis, weight gain and hyperglycemia.

(4) An estimate of patient exposure.

(5) Copies of any correspondence with regulatory authorities regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

(6) The possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

AstraZeneca has now collated and thoroughly assessed all the appropriate data to address each of the above, and full details are provided in this document (Sections 4 to 9).

A summary of preclinical, clinical and postmarketing findings, and an overall conclusion, is provided overleaf.

2 SUMMARY OF DATA

Preclinical data

- A review of all the preclinical data has confirmed that the only salient observations are small changes in glucagon secreting cells in a 1-year rat study with quetiapine fumarate.

  No such changes were observed after administration of quetiapine fumarate at the same dose levels for 2 years in another rat study. Further, no such changes were observed in any of the other species tested in the preclinical program, and no changes in serum glucose levels or pathology indicative of a diabetic condition were observed throughout the preclinical toxicology program.

  Thus the changes observed in the single rat study are considered to be of minimal pathological significance and would not be expected to have any clinical significance in man.

  Overall it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

Clinical data

- The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies and, after adjusting for time-on-study, the incidence of these events did not increase as the duration of exposure to Seroquel increased:
  - cumulative incidence: 1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials (≤ 6 weeks duration), 4.6% in the long-term controlled (> 6 weeks duration) and 3.6% in the uncontrolled trials.
  - incidence density (events/patient-years): 0.6 in the Phase I trials, 0.2 in the short-term controlled trials, 0.2 in the long-term controlled trials and 0.1 in the uncontrolled trials.
- None of the 2419 patients exposed to Seroquel in the clinical trial program were reported as having diabetic ketoacidosis or hyperosmolar coma.
- Only 3 of 2419 patients (0.1%) were reported as having diabetes mellitus (all in the uncontrolled trials). In 2 of the 3 cases, the patients had a past history of diabetes. In the third case, the patient is reported to have 'recovered' from diabetes and continued treatment with Seroquel.

- The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (67 of 2419 patients, 2.8%).

Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program also had diabetes mellitus recorded as an adverse event. This patient had diabetes at baseline (for which they were receiving treatment) and the adverse event of 'poorly controlled diabetes' was subsequently reported.

- There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due to events possibly related to glucose dysregulation; details are as follows:

  - 2 patients were withdrawn for hyperglycemia in the uncontrolled trials. In both cases, the hyperglycemia was considered serious by the Investigator. Both patients had baseline confounding factors: 1 was a known diabetic with a history of hyperglycemia and 1 had a history of borderline glucose levels.

  - 1 patient was withdrawn for weight gain in the short-term controlled trials. The weight gain was not considered serious by the Investigator. Somnolence and abdominal distension were also documented as reasons for withdrawal from treatment in this patient.

  Apart from the 2 adverse events of hyperglycemia above, none of the other events possibly related to disturbances in glucose regulation in the NDA clinical trial program were considered serious by the Investigator.

- There were no statistically significant differences between the Seroquel and placebo groups, Seroquel and chlorpromazine groups (short-term trials) or Seroquel and haloperidol groups (long-term trials) in the mean change from baseline to end of treatment in plasma glucose levels.

- The number of patients treated with Seroquel with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (3.4% in the short-term trials [≤ 6 weeks duration] and 2.9% in the long-term trials [> 6 weeks duration]).

- Where hyperglycemia was observed (glucose value ≥ 200 mg/dl), the condition was not sustained or extreme, and the patients were asymptomatic.

Postmarketing data

- It is estimated that over 623,000 patients have been exposed to Seroquel since its launch in the US in 1997. During this time:
  - no cases of hyperosmolar coma have been reported.
  - 3 cases of diabetic ketoacidosis have been reported. In 2 cases, usage of concomitant medications known to impair glucose tolerance was noted.
  - 12 cases of new-onset diabetes have been reported. In 6 patients, usage of concomitant medications known to impair glucose tolerance was noted.
  - 2 cases of hyperglycemia have been reported.
  - 38 cases of weight gain were reported. Only 2 of the 38 patients with weight gain also had diabetes mellitus.

  Thus very few cases of diabetes mellitus (and related complications), hyperglycemia, and weight gain have been reported. AstraZeneca believes that the current US Seroquel label accurately describes patient experiences to date of these conditions.

3 CONCLUSION

The preclinical data has provided no evidence that Seroquel treatment in man may be associated with diabetes.

The clinical data has shown that the incidence of adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel is low and does not increase as duration of exposure to Seroquel increases. Very few of the adverse events observed were considered serious or led to withdrawal of treatment. There were no cases of diabetic ketoacidosis or hyperosmolar coma and only 3 cases of diabetes mellitus were reported.

A review of the plasma glucose data has revealed similar findings: the hyperglycemia (glucose value ≥ 200 mg/dl) observed in a small number of patients treated with Seroquel was not sustained, extreme, or associated with any symptoms. Further, the incidence of hyperglycemia did not increase as the duration of exposure to Seroquel increased. In addition, there were no statistically significant differences between Seroquel and placebo in the mean changes from baseline to endpoint in plasma glucose levels.

The postmarketing data has shown that even though over 600,000 patients are estimated to have received Seroquel, the number of reported cases of diabetes and related conditions has been extremely small.

Overall, following extensive reviews of all the preclinical, clinical, and postmarketing data, AstraZeneca believes that a diabetogenic potential for Seroquel is unlikely.

4 REVIEW OF PRECLINICAL DATA

In response to Part 1 of the FDA's request, AstraZeneca has completed a comprehensive review of all the preclinical data for evidence of an association between quetiapine fumarate treatment and disturbances in glucose metabolism.

4.1 Salient observations

Hyperplasia of small glucagon secreting cells (alpha cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day dose groups following administration of quetiapine for 12 months to rats (TFR/1626). The changes observed were minimal in severity and were not observed after administration for 2 years at the same dose levels in another rat study (TCR/1624).

No such changes were observed in the pancreatic islets of mice, dogs or primates during single- or multiple- dose studies (of up to 12 months duration) with quetiapine fumarate. In addition, no consistent changes in blood glucose levels occurred during any toxicology study in any species. Further, throughout all the extensive preclinical toxicity studies, there was no degenerative pathology that would reflect the induction of a diabetic state.

4.2 Discussion

A functional change in pancreatic islets might be an expected consequence of administration of a dopamine receptor antagonist that increases circulating prolactin. The lactogenic hormones can modulate pancreatic islet beta-cell function (Landgraf et al 1977, Nielsen JH et al 1982, Michaels RL et al 1987); prolactin stimulates an increase in islet cell protein synthesis leading to an increased secretion of insulin (Markoff et al 1990). Conversely, dopamine agonists decrease the glucose-stimulated release of insulin from beta-cells (Morricone et al 1990, Cavaziel et al 1981). The major physiological importance of glucagon (from alpha-cells) relates to its involvement in metabolic control, where its actions generally oppose that of insulin (Unger et al 1981). Because of its close interrelationship with insulin, many of the drugs that affect beta-cells and insulin also produce effects on alpha cells and glucagon (Woodman 1997).

The above observations in the rat study, together with the literature reports of the effects of dopamine antagonists, would suggest that there is a possibility of quetiapine fumarate affecting islet cell homeostasis. However, no such findings were observed in any of the other species in the toxicology program, and no glucose changes or pathology indicative of a diabetic condition was observed throughout the preclinical program. Thus the hyperplasia of glucagon secreting cells observed in the single rat study appears to be of little or no pathologic consequence and thus does not have the potential for clinical significance.

4.3 Conclusion

A review of all the preclinical data has confirmed that the only salient observations are the small changes in glucagon secreting cells in a 1-year rat study with quetiapine fumarate. This observation is considered to be of minimal pathological significance and would not be expected to have any clinical significance in man.

Overall it is concluded that the preclinical data has provided no evidence that treatment with Seroquel in man may be associated with diabetes.

5 REVIEW OF CLINICAL DATA

In response to Part 2 of the FDA's request, AstraZeneca has thoroughly reviewed the clinical safety database in the Seroquel NDA for evidence of an association between Seroquel treatment and disturbances in glucose metabolism.

5.1 Source material

5.1.1 Adverse event data

In the Seroquel NDA, adverse events were categorized using an in-house dictionary based on the FDA Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). For the purpose of this review, a list of COSTART terms for adverse events that could be related to disturbances in glucose metabolism has been identified, and are as follows:

thirst, polyuria, urinary frequency, weight gain, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, hyperosmolar coma

The incidence of the above events in all of the patients in the Seroquel NDA clinical trial program has been reviewed and assessed in this report. The number of patients exposed to treatment in the Seroquel NDA clinical trial program is presented in Table 1.

Table 1 Summary of clinical trials in the Seroquel NDA integrated database

Pools by trial design	Treatment group and number of patients			
	Seroquel	Placebo	Haloperidol	Chlorpromazine
Phase I	300	0	0	0
Controlled Phase II/III	1710	206	320	100
Short-term (≤ 6 weeks duration)	1450	206	279	100
Long-term (> 6 weeks duration)	260	0	41	0
Uncontrolled	1256	0	0	0
New exposures	409	0	0	0
Patients already counted under previous headings[a]	847	0	0	0
All trials	**2419**	**206**	**320**	**100**

[a] Previously took part in Phase I or controlled Phase II/III trials

In order to observe the effect of an increased duration of exposure to Seroquel on the incidence of the above adverse events, the adverse data in this report have been divided into the following trial pools:

- Phase I trials
  (Seroquel; N=300)
- Short-term controlled Phase II/III trials
  (≤ 6 weeks duration: Seroquel; N=1450, placebo; N=206, haloperidol; N=279, chlorpromazine; N=100)
- Long-term controlled Phase II/III trials
  (> 6 weeks duration: Seroquel; N =260, haloperidol; N=41)
- Uncontrolled Phase II/III trials
  (Seroquel; N=1256)

As the time-on-study in each treatment group will have varied, overall *incidence density* rates, as well as normal cumulative incidence rates, are presented in this report. (Incidence density is defined as the total number of patients with an event, divided by the total patient year exposure).

5.1.2 Plasma glucose data

In the Seroquel NDA, glucose data were collected in 5 trials: 3 short-term placebo-controlled trials (204636/0008, 5077IL/0004, 5077IL/0006), 1 short-term comparator-controlled trial (204636/0007), and 1 long-term comparator-controlled trial (5077IL/0015).

AstraZeneca has been asked by the Agency to provide details on the mean change from baseline in plasma glucose levels, and the number of patients meeting criteria for a markedly abnormal glucose concentration.

5.1.2.1 Mean change from baseline in plasma glucose levels

Mean changes from baseline to end of treatment in plasma glucose levels have been presented for the following trial pools:

- Short-term placebo controlled trials
  (Seroquel; N=230, placebo; N=143)
- Short-term comparator controlled trials
  (Seroquel; N=93, chlorpromazine; N=92)

- Long-term comparator controlled trials
  (Seroquel N=170, haloperidol; N=35)

To observe any statistically significant differences between the treatment groups in each trial pool, the data were analyzed using analysis of covariance, including the baseline score, treatment, center and center-by-treatment interaction as factors. Differences between the treatments were estimated and 95% confidence intervals and p values have been presented.

5.1.2.2 Number of patients meeting criteria for a markedly abnormal plasma glucose level

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) have defined the diagnostic criteria for diabetes as follows: symptoms of diabetes plus a casual plasma glucose concentration ≥ 200 mg/dl; or a fasting blood glucose level equal to or > 126 mg/dl or a 2-hour blood glucose level ≥ 200 mg/dl during an oral glucose tolerance test (Diabetes Care 1997; 20:1183–1197).

In the Seroquel clinical trials, the Investigators were not instructed when to take plasma samples for assessment of glucose levels, and thus the glucose values obtained were *random* values. Therefore, based on the criteria defined by the Expert Committee above, AstraZeneca has defined a markedly abnormal plasma glucose concentration as ≥ 200 mg/dl, at any time.

The number of patients with a plasma glucose concentration of ≥ 200 mg/dl at any time will be summarized by baseline glucose level, as follows:

- patients with a baseline glucose < 200 mg/dl
- patients with a baseline glucose ≥200 mg/dl
- all patients, irrespective of the baseline value

To observe the effect of an increased during of exposure of trial treatment on the number of patient with a markedly high glucose level, the above data will be summarized in 2 trial pools: short-term trials and long-term trials.

In order to analyze plasma glucose values over the course of treatment, and to obtain details on whether the patients had any symptoms of diabetes, detailed profiles of each patient with a plasma glucose level ≥ 200 mg/dl at any time have been obtained and assessed in this report.

As with the adverse event data, in order to adjust for time-on-study, overall incidence density rates, as well as the normal cumulative incidence rates, will be presented for the proportion of patients with a plasma glucose level ≥ 200 mg/dl at any time.

5.2 Results

5.2.1 Adverse event data

5.2.1.1 Phase I trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the Phase I trials are presented in Table 2.

Table 2 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the Phase I trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=300)
Thirst	0
Polyuria	1 (0.3)
Urinary frequency	2 (0.7)
Weight gain[b]	1 (0.3)
Hyperglycemia	1 (0.3)
Diabetes mellitus	0
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**5 (1.7)**
Total number of events	**5**
Total patient year exposure[c]	**8.0**
Incidence density[d]	**0.6**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Only 5 patients (1.7%) had adverse events possibly related to disturbances in glucose metabolism in the Phase I trials. No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. Urinary frequency was the most commonly reported event in these trials.

None of the events in Table 2 were considered serious by the Investigator, or led to withdrawal from treatment.

5.2.1.2 Controlled Phase II/III trials

(a) Short-term trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the short-term controlled Phase II/III trials (≤ 6 weeks duration) is presented in Table 3.

Table 3 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the short-term controlled Phase II/III trials

COSTART term[a]	Number (%) of patients			
	Seroquel (N=1450)	Placebo (N=206)	Haloperidol (N=279)	Chlorpromazine (N=100)
Thirst	3 (0.2)	0	0	0
Polyuria	1 (<0.1)	0	0	1 (1.0)
Urinary frequency	2 (0.1)	0	1 (0.4)	0
Weight gain[b]	20 (1.4)	0	3 (1.1)	0
Hyperglycemia	0	0	0	0
Diabetes mellitus	0	0	0	0
Diabetic ketoacidosis	0	0	0	0
Hyperosmolar coma	0	0	0	0
Total number of patients with events	**24 (1.7)**	**0**	**4 (1.4)**	**1 (1.0)**
Total number of events	**26**	**0**	**4**	**1**
Total patient year exposure[c]	**119.6**	**14.6**	**24.8**	**9.2**
Incidence density[d]	**0.2**	**0**	**0.2**	**0.1**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Twenty-four patients (1.7 %) treated with Seroquel had adverse events possibly related to disturbances in glucose metabolism in the short-term controlled trials. The incidence density was 0.2, which is similar to that observed in the comparator groups.

Two patients each had 2 events in the Seroquel group; 1 patient had thirst and weight gain, and 1 patient had thirst and polyuria.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported. The most frequently reported event in patients treated with Seroquel was weight gain (20 patients, 1.4%); this occurred at a similar incidence as that in the haloperidol group (1.1%).

Of the 20 patients with weight gain in the Seroquel group, 1 patient was withdrawn from treatment due to the weight gain (5077IL/0012/0007/0708). The Investigator did not considered this event to be serious. A review of this patient's details revealed that, in addition to weight gain (2.0 kg over 2 weeks), this patient also withdrew for reasons of somnolence and abdominal distension. A full narrative of this patient is presented in Appendix A.

Apart from the 1 case of weight gain discussed above, none of the other events in Table 3 led to a patient being withdrawn from treatment or were considered serious by the Investigator.

(b) Long-term trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the long-term controlled Phase II/III trials (> 6 weeks duration) is presented in Table 4.

Table 4 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the long-term-controlled Phase II/III trials

COSTART term[a]	Number (%) of patients	
	Seroquel (N=260)	Haloperidol (N=41)
Thirst	1 (0.3)	0
Polyuria	0	0
Urinary frequency	0	0
Weight gain[b]	11 (4.2)	0
Hyperglycemia	0	0
Diabetes mellitus	0	0
Diabetic ketoacidosis	0	0
Hyperosmolar coma	0	0
Total number of patients with events	**12 (4.6)**	**0**
Total number of events	**12**	**0**
Total patient year exposure[c]	**79.3**	**17.6**
Incidence density[d]	**0.2**	**0**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

Twelve patients (4.6%) treated with Seroquel had adverse events possibly related to disturbances in glucose metabolism in the long-term controlled trials. The incidence density was 0.2, which is the same as that observed in the short-term trials (Table 3), indicating that the incidence of adverse events possibly related to disturbances in glucose metabolism does not increase as duration of exposure to Seroquel increases.

No cases of diabetes mellitus, diabetic ketoacidosis or hyperosmolar coma were reported in either treatment group. Weight gain was the most frequently reported event in the Seroquel group.

None of the events in Table 4 were considered serious by the Investigator, or led to withdrawal from treatment.

5.2.1.3 Uncontrolled Phase II/III trials

The number (%) of patients with adverse events possibly related to disturbances in glucose metabolism across the uncontrolled Phase II/III trials are presented in Table 5.

Table 5 Number (%) of patients with adverse events possibly related to disturbances in glucose metabolism in the uncontrolled Phase II/III trials

COSTART term[a]	Number (%) of patients
	Seroquel (N=1256)
Thirst	1 (0.1)
Polyuria	1 (0.1)
Urinary frequency	3 (0.2)
Weight gain[b]	38 (3.0)
Hyperglycemia	2 (0.2)
Diabetes mellitus	3 (0.2)
Diabetic ketoacidosis	0
Hyperosmolar coma	0
Total number of patients with events	**45 (3.6)**
Total number of events	**48**
Total patient year exposure[c]	**386.2**
Incidence density[d]	**0.1**

[a] Each patient may have more than 1 adverse event
[b] Any weight gain event, irrespective of the magnitude of the gain
[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with events divided by the total patient year exposure

In total, 3.6 % of patients had adverse events possibly associated with disturbances in glucose regulation in the uncontrolled trials.

Three patients each had 2 events: 1 patient had hyperglycemia and urinary frequency, 1 patient had thirst and polyuria and 1 patient had diabetes mellitus and weight gain. Weight gain was the most frequently reported event in these trials.

No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Three cases (0.2%) of diabetes mellitus were reported. Full narratives for each patient are presented in Appendix A. In

2 cases (5077IL/0012/0046/4603 and 5077IL/0015/0005/0509), the patients had a history of diabetes. In the final case (5077IL/0014/0036/3605), the patient is reported to have 'recovered' from the diabetes whilst on Seroquel treatment following treatment with glibenclamide. None of the cases of diabetes mellitus were considered by the Investigator to be related to trial therapy. In addition, none of the 3 cases were considered by the Investigator to be serious, or led to withdrawal of treatment.

Two patients had hyperglycemia in these trials. In both cases, the Investigator considered the events to be serious, and the patients were withdrawn from treatment. Full narratives of both patients are presented in Appendix A. Both patients had significant confounding factors: 1 patient (5077IL/0012/0093/9304) had a history of hyperglycemia and diabetes and the other patient (5077IL/0013/0001/0109) had a history of borderline elevated glucose levels. Neither case was considered by the Investigator to be related to treatment with Seroquel.

Apart from the discussed above, none of the other events in Table 5 were considered to be serious by the Investigator, or led to withdrawal from treatment.

5.2.2 Plasma glucose data

5.2.2.1 Mean change from baseline in random plasma glucose levels

The mean changes from baseline to the end of treatment in plasma glucose levels are presented in Table 6 (placebo-controlled trials), Table 7 (short-term comparator-controlled trials) and Table 8 (long-term comparator-controlled trials).

Table 6 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term placebo-controlled trials

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	230	3.60	1.52					
Placebo	143	-0.26	1.93					
Seroquel versus placebo				3.87	2.46	-0.97	8.71	0.1173

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

Table 7 Mean change from baseline to end of treatment in plasma glucose levels (random values) in short-term comparator-controlled trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	93	-1.30	1.98					
Chlorpromazine	92	-1.20	1.99					
Seroquel versus chlorpromazine				-0.10	2.81	-5.64	5.44	0.9721

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

Table 8 Mean change from baseline to end of treatment in plasma glucose levels (random values) in long-term trial

Treatment	N	Mean change from baseline (mg/dl)		Difference between treatments				
		LSMean	SE	DIFF (mg/dl)	SE	LCL	UCL	p-value
Seroquel	170	4.53	2.57					
Haloperidol	35	4.01	5.68					
Seroquel versus haloperidol				0.52	6.24	-11.79	12/83	0.9333

LS Least squares mean SE Standard error Diff Difference between treatments
LCL Lower 95% confidence limit UCL Upper 95%confidence limit
N is based on the number of patients with both baseline and end of treatment glucose data

The differences between the treatment groups within each trial pool were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine or Seroquel versus haloperidol).

5.2.2.2 Number of patients meeting criteria for a markedly abnormal plasma glucose level

The number of patients with a plasma glucose level ≥200 mg/dl at any time postbaseline has been summarized in Table 9 (short-term trials) and Table 10 (long-term trials), according to the baseline glucose level.

Table 9 Number (%) of patients with glucose ≥ 200 mg/dl (random values) in short-term trials[a]

Baseline glucose level	Treatment group		
	Seroquel (N=323)	Placebo (N=143)	Chlorpromazine (N=92)
Number of patients with baseline glucose < 200 mg/dl	322	142	92
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	10 (3.1)	1 (0.7)	0
Number of patients with baseline glucose > 200 mg/dl	1	1	0
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	1 (100%)	0 (0)	0
All patients, irrespective of baseline glucose value	**323**	**143**	**92**
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	**11 (3.4)**	**1 (0.7)**	**0**
Total patient year exposure[c]	**28.1**	**10.6**	**8.8**
Incidence density[d]	**0.4**	**0.1**	**0**

[a] From Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006

[b] % uses total number of patients in baseline sub-group as a denominator

[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365

[d] Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dl at any time divided by the total patient year exposure N is based on the number of patients with both baseline and end of treatment glucose data

Table 10 Number (%) of patients with glucose ≥ 200 mg/dl (random values) in long-term trials[a]

Baseline glucose level	Treatment group	
	Seroquel (N=170)	Haloperidol (N=35)
Number of patients with baseline glucose < 200 mg/dl	167	32
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	2 (1.2)	1 (3.1)
Number of patients with baseline glucose > 200 mg/dl	3	3
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	3 (100)	2 (66.7)
All patients, irrespective of baseline glucose value	**170**	**35**
Number (%[b]) of patients with glucose ≥ 200 mg/dl post-baseline	**5 (2.9)**	**3 (8.6)**
Total patient year exposure[c]	**68.1**	**16.4**
Incidence density[d]	**0.1**	**0.2**

[a] From Trials 204636/0007, 204636/0008, 5077IL/0004, 5077IL/0006
[b] % uses total number of patients in baseline subgroup as a denominator

[c] Total patient year exposure is defined as the sum of days on treatment for each patient, divided by 365
[d] Incidence density is defined as the total number of patients with glucose ≥ 200 mg/dl at any time divided by the total patient year exposure
N is based on the number of patients with both baseline and end of treatment glucose data

The proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the short-term trials was low in all treatment groups (an incidence density of 0.4, 0.1 and 0 in the Seroquel, placebo and chlorpromazine groups, respectively). Similarly, the proportion of patients with a postbaseline glucose value ≥ 200 mg/dl in the long-term trials was low in both treatment groups (an incidence density of 0.1 and 0.2 in the Seroquel and haloperidol groups, respectively).

The proportion of patients a postbaseline glucose value ≥ 200 mg/dl did not increase as duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

These data were based on random plasma glucose assessments and are therefore expected to fluctuate depending on the interval since the last meal, glucose content of the last meal, the state of hydration of the patient and many other factors. In order to make a thorough assessment on the effect of Seroquel treatment on plasma glucose levels, narratives of all patients with a glucose value ≥ 200 mg/dl at any time have been prepared and analyzed to assess whether the elevated levels were consistent or sporadic, whether they were extreme, and whether any of the patients concerned had symptoms of diabetes. Full details are provided below.

In total, 20 patients had a plasma glucose level ≥ 200 mg/dl. Of these, 3 patients received haloperidol, 1 patient received placebo and 16 patients received Seroquel. Narratives of all 20 patients are provided in Appendix A.

Three patients who received haloperidol (0012/1205,0021,2105, 0035/3502) had post baseline glucose values >200mg/dl. Two of them had baseline glucose values >200mg/dl and all 3 had histories of hyperglycemia or diabetes.

The single placebo patient with post baseline hyperglycemia had a baseline glucose of 142 mg/dl. Four of 6 post baseline assessments including the final assessment were in excess of 200mg/dl.

A review of the 16 patients who received Seroquel does not suggest a diabetogenic effect of Seroquel, as discussed below:

(a) Patients with a baseline glucose value < 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Twelve of the 16 patients treated with Seroquel had a baseline glucose value < 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl.

In only 5 of the 12 patients was the last glucose value >200mg/dl. In 3 of these 5 patients (0001/0021,0026/2607 and 0034/3411) the baseline value was elevated and slightly less than 200mg/dl (178mg/dl, 192mg/dl and 186mg/dl, respectively). In the remaining 2 patients, repeated hyperglycemia was not observed since only the last glucose determination was ≥200mg/dl.

Seven of the 12 patients had baseline glucose values <200mg/dl, a last glucose of <200mg/dl and at least 1 post baseline assessment of ≥200mg/dl. In 6 of these 7 patients only 1 of several post-baseline assessments was ≥200mg/dl. In the seventh of these patients 3 of 6 determinations were ≥200mg/dl, but the last glucose value was 149.5 mg/dl, only 7.2mg/dl greater than the baseline value.

None of these 12 patients had a blood glucose determination >300mg/dl.

Thus in these 12 patients, sustained hyperglycemia was not observed and the sporadic glucose elevations were not extreme. Further, *none* of the patients had classic symptoms of diabetes, such as polyuria, polydipsia and unexplained weight loss. The glucose values observed are plausibly understood as variations in a parameter that is strongly influenced by the interval since the last meal, glucose content of the last meal, state of hydration and many other factors.

(b) Patients with a baseline glucose value ≥ 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl

Four of the 16 patients treated with Seroquel had a baseline glucose value ≥ 200 mg/dl and at least 1 post-baseline glucose value ≥ 200 mg/dl. Two of the 4 patients (0019/1903, 0023/2310) had a history of diabetes. A third had a history of hypothyroidism (0013/1309). The fourth patient's (0020/0005) final blood glucose was lower than baseline.

5.3 Discussion

5.3.1 Adverse event data

The incidence of patients with adverse events possibly related to disturbances in glucose regulation in patients treated with Seroquel was low across all studies (1.7 % in the Phase I trials, 1.7% in the short-term Phase II/III trials [≤ 6 weeks duration], 4.6% in the long-term controlled [> 6 weeks duration] and 3.6% in the uncontrolled trials).

After adjusting for time-on-study, the incidence of adverse events possibly related to disturbances in glucose metabolism did not increase as the duration of exposure to Seroquel increased (incidence density of 0.6 for the Phase I trials, 0.2 for the short-term controlled trials, 0.2 for the long-term controlled trials and 0.1 for the uncontrolled trials).

A total of 2419 patients was exposed to Seroquel across the Phase I, short- and long-term controlled Phase II/III, and uncontrolled trials in the Seroquel NDA. No cases of diabetic ketoacidosis or hyperosmolar coma were reported. Diabetes mellitus was reported in just 3 (0.1%) patients (5077IL/0012/0046/4603, 5077IL/0014/0036/3605 and 5077IL/0015/0005/0509, Appendix A). All 3 cases were reported in the uncontrolled trials. Two of the 3 patients had a history of diabetes. The third patient is reported to have 'recovered' from the diabetes following treatment with glibenclamide and continued treatment with Seroquel. None of the cases of diabetes mellitus were considered by the Investigator to be related to trial therapy. Further, none of the cases were considered serious by the Investigator or led to withdrawal of treatment.

The most frequently reported event in patients treated with Seroquel (in this class of events) was weight gain (67 of 2419 patients, 2.8%). Obesity can be a risk factor for diabetes. However, only 1 of the 67 patients with weight gain in the clinical trial program had diabetes mellitus (5077IL/0015/0005/0509, Appendix A). This patient had diabetes at baseline (for which they were receiving treatment) and subsequently had 'poorly controlled' diabetes recorded as an adverse event. These observations would indicate that weight gain in patients treated with Seroquel is not a risk factor for the development of diabetes. This is not surprising, as our latest analyses have shown that the actual weight gain associated with Seroquel treatment is minimal, even in the long-term (a mean gain of 1.87 kg [median 1.20 kg] over 1.5 years is observed; for further details see Appendix C). It should be noted that AstraZeneca has already alerted the Prescriber to the possibility of weight gain with Seroquel via the inclusion of a statement in the US Prescribing Information.

There were no deaths due to adverse events possibly related to disturbances in glucose regulation. Only 3 of 2419 patients (0.1%) were withdrawn from treatment due events possibly related to glucose dysregulation.

Two patients were withdrawn from treatment due to hyperglycemia (in the uncontrolled trials); both events were considered serious by the Investigator. One of these patients (5077IL/0012/0093/9303, Appendix A) was a known diabetic with a history of hyperglycemia before entering the trial, and the other patient (5077IL/0013/0001/0109, Appendix A) had a history of borderline elevated glucose levels. The investigator did not consider either case to be related to treatment with Seroquel. One patient was withdrawn from treatment due to weight gain (in the short-term controlled trials). Somnolence and abdominal distension were also documented as reasons for withdrawal in this patient. The event was not considered serious by the Investigator.

Apart from the 2 cases of hyperglycemia, none of the other events possibly related to disturbances in glucose regulation in the clinical trial program were considered serious by the Investigator.

5.3.2 Plasma glucose data

The differences between the treatment groups in the mean change from baseline in plasma glucose data in short-term trials and long-term trials were small. There was a wide variability in the results, as expected from blood samples collected at unspecified times after meals. There were no statistically significant differences between any of the treatment groups in each trial pool (Seroquel versus placebo, Seroquel versus chlorpromazine [short-term trial] or Seroquel versus haloperidol[long-term trial]).

The proportion of patients with a glucose value ≥ 200 mg/dl at any time was low and did not increase as the duration of exposure to Seroquel increased (an incidence density of 0.4 in the short-term trials, compared with 0.1 in the long-term trials).

A detailed review of the patients with a glucose value ≥ 200 mg/dl revealed that the majority of elevations were sporadic (ie not consistently observed during treatment) and did not exceed 300 mg/dl at any time. Further, *none* of the patients had symptoms of diabetes. It is likely that the values observed reflect variations in a parameter that is strongly influenced by the interval since that last meal, glucose content of the last meal, state of hydration, and many other factors.

5.4 Conclusion

In conclusion, a thorough review of all the adverse event data and plasma glucose data in the clinical trial program has revealed no clear evidence of a causal association between Seroquel treatment and disturbances in glucose regulation. In addition, there was no evidence from the clinical data of a direct link between weight gain in patients treated with Seroquel and the onset of diabetes.

6 REVIEW OF POSTMARKETING DATA

In response to Part 3 of the FDA's request, spontaneous postmarketing reports received by AstraZeneca since Seroquel's US approval (September 1997) up to May 2000 have been thoroughly reviewed for possible cases of hyperosmolar coma, new-onset diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain.

6.1 Results

6.1.1 Hyperosmolar coma

There have been no postmarketing reports of hyperosmolar coma.

6.1.2 New-onset diabetes mellitus

There have been 12 spontaneous postmarketing reports of new-onset diabetes mellitus (including 2 literature reports). Narratives of all 12 patients are presented in Appendix B.

The age range for patients with new onset diabetes mellitus is 12 to 48 years, with an average age at onset of 32.5 years (median = 34 years). There is a male predominance, with males constituting 75% of all reports. Daily Seroquel dosages ranged from 50 mg to 750 mg, with an average daily dose of 385 mg (median = 400 mg). The average time interval between initial therapy and the date of the reported event was 4.9 months with a range of 15 days to 21 months (median = 2.0 months). Blood glucose concentrations at clinical presentation averaged 833 mg/dl and ranged from 311 to 2240 mg/dl (median 474= mg/dl).

Weight gain was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 1999UW03532).

Weight loss was reported in 1 of the 12 patients with new-onset diabetes (2000UW01164).

Diabetic ketoacidosis was reported in 2 of the 12 patients with new-onset diabetes (1999AP05757 and 2000UW01164).

Dose-related loss of glycemic control was reported in 2 of the 12 patients with new-onset diabetes mellitus (1999UW00969 and 1998UW48512).

One patient developed Type 1 diabetes mellitus (2000UW00266).

In addition to the 12 patients with new-onset diabetes described above, AstraZeneca has received 4 reports describing exacerbation of pre-existing diabetes mellitus.

6.1.3 Diabetic ketoacidosis

There have been 3 postmarketing spontaneous reports of diabetic ketoacidosis. Narratives of all 3 patients are presented in Appendix B.

The age range is 25 to 58 with an average age at onset of 42 years (median= 43 years). All 3 patients were male. Daily Seroquel dosages ranged from 200 mg to 800 mg, with an average daily dose of 583 mg (median = 750 mg). The average time interval between initial therapy and the date of the reported event was 11.0 months with a range of 1 to 21 months (median =11 months). Blood glucose concentrations at clinical presentation for these patients were not provided.

Two of the 3 patients with diabetic ketoacidosis also developed new-onset diabetes mellitus. (1999AP05757 and 2000UW01164). The former patient gained an unspecified amount of weight and the latter patient lost 13.6 kg.

Another patient (1998UW49554) with a pre-existing diabetic condition died due to complications of diabetes mellitus.

6.1.4 Hyperglycemia

There have been 2 postmarketing spontaneous reports of hyperglycemia. Narratives of both patients are presented in Appendix B.

Blood glucose concentrations were not provided for either patient. One report (2000UW01047) involved a 47-year-old female who developed weight gain and hyperglycemia after taking Seroquel 150 mg daily for 30 months. The other report (1998AP50408) contains scant information, except the daily Seroquel dose which was 750 mg.

6.1.5 Weight gain

There have been 38 spontaneous postmarketing reports and 4 literature reports of weight gain associated with Seroquel therapy.

Patients ranged in age from 8 to 70 years of age with a mean of 38 years (median = 36 years). There is a slight female predominance with females constituting 55% of reports in which gender was specified. Reported weight gain ranged from 0.9 kg to 31.8 kg with the average reported weight gain being 12.5 kg (median = 10.7 kg). The average time interval between initial therapy and the date of the reported event was 6.8 months with a range of 10 days (2.2 kg) to 2 years (18.1 kg) and a median of 4 months.

Diabetes mellitus was reported in 2 of the 38 patients with weight gain (1999AP05757 and 1999UW03532).

6.2 Discussion

Since the approval of Seroquel in the US in September 1997, it is estimated that over 623,000 patients have been exposed to Seroquel (see Section 7). Despite this extensive exposure, only a small number of cases of diabetes mellitus, diabetic ketoacidosis, hyperglycemia and weight gain have been reported.

Many of the cases reported had confounding factors. Six of the 12 patients with new-onset diabetes were reported as using concomitant medications known to be associated with glucose dysregulation and diabetes mellitus, including risperidone, fluoxetine, albuterol, and venlafaxine (2000UW01164, 1999UW03387, 1999AP02989, 1999AP05218, 1998UW48512, and 1999UW00969). Few, if any, of the 12 patients had baseline fasting glucose levels.

One of the 3 patients with diabetic ketoacidosis (2000UW01164) is reported to have used concomitant medications known to impair glucose tolerance and cause diabetes mellitus (venlafaxine). Another patient (1998UW49554) had a pre-existing diabetic condition.

In the patients with weight gain, there are several confounding factors to note. Two patients (1999UW01496 and 1998UW46392) developed edema and 1 patient (1999AP00761) was diagnosed with congestive heart failure. Edema and heart failure are both labeled adverse events that are known to contribute to weight gain secondary to fluid retention and accumulation. There was 1 report (1999UW02120) describing a negative dechallenge in which the accrued weight remained despite discontinuation of Seroquel treatment. Two patients (1999UW02120 and 1998UW48690) had concomitant hypothyroidism, a known cause for weight gain. In addition, 1 patient (1999AP05242) developed hypothyroidism after starting Seroquel treatment.

Unfortunately, several postmarketing reports contained only scant information that precluded further detailed analysis of these cases.

The current US Seroquel package insert is labeled for diabetes mellitus, hyperglycemia, and weight gain as Adverse Reactions. Details are provided below.

Under the category of Other Adverse Events Observed During the Pre-marketing Evaluation of SEROQUEL in the insert, diabetes and hyperglycemia are listed as an infrequent experience (events occurring in 1/100 to 1/1000 patients). Weight gain (2%) is included as a treatment-emergent adverse experience in 3- to 6-week placebo-controlled clinical trials. The package insert also alerts the Prescriber to a statistically significantly greater incidence of weight gain (≥ 7% of body weight) for SEROQUEL (23%) compared to placebo (8%). In addition, reference is made

to spontaneously elicited adverse event data from a study comparing five fixed doses of Seroquel (75 mg, 150 mg, 300 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. The insert states that logistic regression analysis revealed a positive dose response ($p < 0.05$) for weight gain in this analysis.

The package insert does not contain any details of diabetic ketoacidosis or hyperosmolar coma. However, only 3 spontaneous reports of diabetic ketoacidosis have been received to date in patients using Seroquel (indicating that there does not appear to be a signal that Seroquel is associated with diabetic ketoacidosis) and there have been no reported cases of hyperosmolar coma.

AstraZeneca has paid particular attention to the incidence of patients with both weight gain and diabetes. Only 2 patients were reported to have had concomitant weight gain and diabetes mellitus. Thus there does not appear to be a link between these 2 conditions.

6.3 Conclusion

It is concluded that that the current Seroquel package label accurately describes patient experiences to date of diabetes mellitus (and related complications), hyperglycemia, and weight gain.

7 PATIENT EXPOSURE ESTIMATION

In response to Part 4 of the FDA's request, AstraZeneca has calculated the extent of exposure to Seroquel across the clinical trial program, and estimated the extent of exposure to Seroquel from postmarketing experience.

7.1 Clinical trials

7.1.1 Phase I trials

A total of 300 patients were exposed to Seroquel in the Phase I trials.

The mean daily dose and duration of Seroquel use in the Phase I clinical trials are presented in Table 11.

Table 11 Mean daily dose and duration of exposure to Seroquel in the Phase I trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	33	0	0	0	0	0	33 (11)
2 to 7	83	5	10	1	0	0	99 (33)
8 to 14	1	3	19	18	29	0	70 (23)
15-21	0	0	21	46	9	7	83 (28)
22-35	0	8	1	5	1	0	15 (5)
Total (%)	117 (39)	16 (5)	51 (17)	70 (23)	39 (13)	7 (2)	300 (100)

Approximately 40% of subjects received Seroquel for less than 7 days. A total of 55% of subjects had mean doses of Seroquel within the clinically effective dose range (>150 to < 800 mg/day). Fifteen percent of subjects had mean daily doses that were greater than 450 mg/day.

7.1.2 Controlled Phase II/III trials

A total of 1710 patients were exposed to Seroquel in the controlled Phase II/III trials.

The mean daily dose and duration of Seroquel use in the controlled Phase II/III clinical trials are presented in Table 12.

Table 12 Mean daily dose and duration of exposure to Seroquel in the controlled Phase II/III trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	14	0	0	0	1	0	15 (1)
2 to 7	59	24	60	4	1	0	148 (9)
8 to 14	63	17	60	79	21	2	242 (14)
15 to 21	36	22	37	55	19	2	171 (10)
22 to 28	23	6	23	40	19	1	112 (7)
29 to 35	17	2	16	24	9	8	76 (4)
36 to 42	97	26	94	285	138	63	703 (41)
43 to 112	39	6	29	51	27	9	161 (9)
113 to 183	5	0	7	0	9	0	21 (1)
184 to 365	16	4	15	0	20	0	55 (3)
366 to 548	0	0	2	0	3	1	6 (0)
Total (%)	369 (22)	107 (6)	343 (20)	538 (32)	267 (16)	86 (5)	1710 (100)

Most subjects (86%) received Seroquel for 6 weeks or less because most exposure in the controlled trials occurred in short-term trials. The majority of subjects (72%) had mean daily doses of Seroquel that were greater than 150 mg/day; 21% had mean daily doses that were greater than 450 mg/day.

7.1.3 Uncontrolled Phase II/III trials

A total of 1256 patients were exposed to Seroquel in the uncontrolled trials. Of these, 847 patients had taken part in the controlled trial program.

The mean daily dose and duration of Seroquel use in the uncontrolled Phase I/III clinical trials are presented in Table 13.

Table 13 Mean daily dose and duration of exposure to Seroquel in the uncontrolled trials

Duration (days)	Mean daily dose of Seroquel (mg)						Total (%)
	≤ 75	> 75 ≤ 150	> 150 ≤ 300	> 300 ≤ 450	> 450 ≤ 600	> 600 ≤ 800	
1	6	1	1	0	0	0	8(1)
2 to 7	17	18	31	11	2	1	80(6)
8 to 14	7	4	27	19	22	7	86 (7)
15 to 21	7	2	10	30	25	15	89 (7)
22 to 28	8	5	25	40	28	18	124 (10)
29 to 35	2	2	5	15	29	13	66 (5)
36 to 42	3	6	10	10	14	14	57 (5)
43 to 112	10	12	36	57	80	82	277 (22)
113 to 183	1	2	24	49	65	46	187 (15)
184 to 365	1	5	41	58	60	62	227 (18)
366 to 548	0	1	8	10	16	17	52 (4)
549 to 730	0	0	1	0	0	1	2 (0)
730	0	0	0	0	0	1	1 (0)
Total (%)	62 (5)	58 (5)	219 (17)	299 (24)	341 (27)	277 (22)	1256 (100)

A total of 59% of subjects had been given Seroquel for longer than 6 weeks: 282 subjects were exposed to Seroquel for 6 months or longer, 55 subjects were exposed for more than 1 year and 1 subject was exposed to Seroquel for more than 2 years. Most subjects (90%) had mean daily doses of Seroquel that were greater than 150 mg/day, whereas 49% of subjects had mean daily doses greater than 450 mg/day.

7.2 Postmarketing experience

It is difficult to obtain a precise estimate of the number of patients that have been exposed to Seroquel since launch. However, a recent audit of the NDC database indicated that, on average, a patient received 3.84 prescriptions for Seroquel. In post-launch period to 30 June 2000, 2,393,000 prescriptions have been written for Seroquel in the US. This would suggest that approximately 623,000 unique patients have been exposed to Seroquel since launch, representing approximately 199,000 patient years (assuming that each prescription covers a 1- month period).

8 CORRESPONDENCE WITH REGULATORY AGENCIES

In response to Part 5 of the FDA's request, AstraZeneca has reviewed all correspondence with regulatory agencies regarding events related to possible disturbances in glucose metabolism associated with Seroquel.

8.1 Results

There have been no issues raised verbally or formally in correspondence with foreign regulatory agencies related to the events of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, and hyperglycemia associated with Seroquel.

Questions relating to weight gain during the clinical program were asked by the French and Swiss agencies during their national reviews and also by Spain during the question and answer period in the European Mutual Recognition (MR) procedure conducted in the latter half of 1999.

In preclinical assessment, the Swedish Medical Products Agency (MPA) and the Japanese Ministry of Health and Welfare (MHW) asked the same question during their national reviews regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study. This topic is also addressed in Part 1 of this FDA response.

Copies of all the questions and company responses are provided in Appendix D.

8.2 Discussion

In terms of weight gain, it should be noted that the company has already taken the step globally of alerting the Prescriber to the possibility of limited weight gain with Seroquel via the inclusion of a statement in Section 4.9 (possible adverse reactions) of the Core Data Sheet for the product.

In the spirit of this, the Adverse Reactions section of the US Professional Information Brochure advises the physician that there is a statistically significantly greater incidence of weight gain for Seroquel (23%) compared to placebo (6%).

The explanation given to both MPA and MHW regarding the mechanism of hyperplasia of glucagon secreting cells in the pancreas in the 1 year rat study was accepted by both agencies.

9 POTENTIAL COLLABORATION WITH OTHER DATABASES

We are investigating the possibility of collaborating with organizations having large pools of treated patients that might be examined for evidence of hyperglycemia or new-onset diabetes associated with Seroquel.

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APPENDIX A

Patient narratives: clinical data

Patients withdrawn from treatment due to adverse events possibly associated with disturbances in glucose metabolism

5077IL/0012/ 0007/0708 Seroquel

Abdomen enlarged, Weight gain, Somnolence

This 37-year old, white woman with chronic paranoid schizophrenia was withdrawn on Day 10 for abdominal distension, abnormal weight gain, and drowsiness while receiving Seroquel 450 mg/day, administered on a twice-daily basis. The drowsiness resolved 1 day later. Her weight gain was 2.0 kg over 2 weeks, and returned to pretrial levels 6 days after withdrawal, as did the abdominal distension. She was receiving no concurrent medication at entry and had an unremarkable medical history other than tubal ligation. The abdominal distension, abnormal weight gain, and drowsiness were considered by the investigator to be probably related to Seroquel.

5077IL/0012/ 0093/9304 Seroquel

Hyperglycemia

This 53-year-old, white woman with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 34 (Seroquel 200 mg/day) due to hyperglycemia (glucose value not available). The subject was a known diabetic and had hyperglycemia noted prior to entry into the trial. Other significant medical history included hypertonia and angina. Concurrent medications included ascorbic acid/ferrous sulfate combination, insulin protamine injection/insulin regular combination, glycerol trinitrate, fenofibrate, REDACTED, insulin protamine injection, insulin regular, and drotaverine. On Day 18 (Seroquel 200 mg/day), hyperglycemia (COSTART term hyperglycemia) was reported as an adverse event (glucose value not available). The hyperglycemia resolved 3 weeks (Day 55) after withdrawal from trial treatment. The event was considered by the investigator to be moderate in intensity and probably not related to trial treatment.

5077IL/0013/ 0001/0109 Seroquel

Hyperglycemia

This 44-year-old, black man with a diagnosis of chronic paranoid schizophrenia was withdrawn from trial treatment on Day 10 (Seroquel 150 mg/day) due to hyperglycemia. Medical history was significant for borderline elevated glucose levels (untreated), Bell's palsy, back pain, gynecomastia, peptic ulcer disease, hiatal hernia, obesity, abdominal discomfort, and urinary hesitancy. Concurrent medications included ranitidine, pseudophedrine/triprolidine combination, and glipizide. On Day 8, the fasting blood glucose level previously drawn was discovered to be 392.72 mg/dl (normal range 68 to 115 mg/dl). A repeat level drawn on Day 8 was 407.1 mg/dl. The subject was sent to the emergency room for a medical consult, where he was started on glipizide and placed on a special diet prior to his return to the unit that same day. On Day 10 (Seroquel 600 mg), he complained of nausea, dizziness, and blurred vision, and vomited his lunch. A blood glucose level was immediately drawn with a result of 1104.3 mg/dl. The subject was again transferred to the emergency room and was admitted to the medical intensive care unit of the hospital, where he was started on intravenous insulin and hydration. At this time, trial treatment was discontinued. By Day 11, his blood glucose had decreased to the 198.1 mg/dl range and the subject had otherwise returned to his baseline health. The insulin drip was discontinued on Day 12 and he was maintained on subcutaneous insulin until Day 15, when this was switched to glyburide and he was transferred back to his original unit. Glucose remained stable in the 198.1 mg/dl range. The subject did not receive any further trial treatment after Day 10 due to difficulties in following the subject at another hospital. The investigator considered restarting the subject on the trial treatment once he returned to his original unit; however, at the request of the subject's spouse, this was not done. The investigator considered the hyperglycemia to be severe in intensity and not related to trial treatment.

Patients with adverse events of diabetes mellitus

5077IL/0012/0046/4603 Seroquel (controlled trials), Seroquel (open label extension)

This patient is a 35-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day. The patient had a history of eye esotropia and diabetes mellitus. The patient was receiving daonil for diabetes before the start of the trial. During the trial adverse events of weakness, sleepiness and constipation were all reported as mild and possibly related. The patient discontinued Seroquel therapy at a dose of 450 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of headache, insomnia and unstable diabetes were reported. The unstable diabetes was reported 9 days into open label treatment. The patient was receiving 300 mg/day Seroquel. The event was considered 'moderate' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed insulin and glucophage for the diabetes.

5077Il/0014/0036/3605 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 51-year old white female presenting with paranoid schizophrenia who began haloperidol at a dose of 1mg/day. The patient had a past history of hypertension.

During the trial the adverse event of moderate hypertension, related to therapy, was recorded. The patient discontinued haloperidol therapy at a dose of 10 mg/day on Day 41. The reason for discontinuation was reported as 'completed protocol'.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of diabetes mellitus and infection were reported. The diabetes mellitus was reported 61 days into open label treatment. The patient was receiving 400 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide for the diabetes.

5077IL/0015/0005/0509 Haloperidol (controlled trials), Seroquel (open label extension)

This patient is a 40-year old black female presenting with paranoid schizophrenia who began haloperidol at a dose of 2 mg/day. She had a medical history of otitis media, tooth infections, chronic headaches, EPS (benzatropine), cardiomegally (mild hypertension), bronchitis, urinary tract infection (salpingeltomy), diabetes, depression (nortriptyline), anxiety (lorazepam), insomnia (chloral hydrate). The patient was prescribed glibenclamide for the diabetes before the trial.

During the trial adverse events of hand tremors, muscle stiffness and cogwheel rigidity were all reported as moderate and probably related were reported. The patient discontinued haloperidol therapy at a dose of 12 mg/day on Day 28. The reason for discontinuation was reported as adverse reaction/intercurrent illness.

On trial completion the patient entered an open label extension trial with Seroquel. During this time, adverse events of tongue tremors, constipation, weight gain, tooth abscess, septicemia, insomnia and poorly controlled diabetes mellitus were reported. The diabetes mellitus was reported 344 days into open label treatment. The patient was receiving 500 mg/day Seroquel. The event was considered 'mild' in nature. The event was not considered serious and did not lead to withdrawal from treatment. The investigator did not consider the event to be related to trial treatment. The patient was prescribed glibenclamide and received insulin injections for the diabetes.

Patients with plasma glucose ≥ 200 mg/dl at any time

204636/0007/0003/0002 Seroquel

This patient is a 35-year old white female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 50mg/day on 16-May-1991(Day 0). She had a medical history of anemia (ferrous sulfate, folic acid), psychosis (lithium carbonate, stelazine) and depression (lofepramine). Pre-trial antipsychotic medication was not recorded. She received EPS medications -unspecified (agitation), benzodiazepines (agitation) and chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 1000mg/day by Day 19. The patient's weight was 63.0kg on Day 0 and 66.0kg on Day 27.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
15-May-91 (1)	162
23-May-91 (7)	133.3
30-May-91 (14)	221.6
05-Jun-91 (20)	97.3
12-Jun-91 (27)	86.5

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'treatment failure'.

204636/0008/0001/0021 Seroquel

This patient is a 21-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 05-Aug-1991(Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 76.2kg on Day 0 and 76.2kg on Day 10.

During treatment adverse events of drowsiness, depressed thyroid stimulation, thyroxine and triiodothyronine were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
26-July-91 (-10)	178.3
12-Aug-91 (7)	207.2

The patient discontinued Seroquel therapy at a dose of 50 mg/day on Day 10. The reason for discontinuation was reported as 'refused to continue'.

204636/0008/0005/0003 Seroquel

This patient is a 55-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-Sept-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 6. The patient's weight was 81.0kg on Day 0 and 82.0kg on Day 41.

During treatment an adverse event of severe agitation which was possibly related was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
29-Aug-91 (-4)	167.5
17-Sept-91 (15)	210.8
23-Sept-91 (21)	196.4
01-Oct-91 (29)	129.7
09-Oct-91 (37)	106.3
14-Oct-91 (42)	90.1

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0009/0002 Seroquel

This patient is a 59-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 50mg/day on 20-Aug-1991 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded.

During the trial the patient was dosed Seroquel up to a level of 350mg/day by Day 13. The patient's weight was 88.9kg on Day 0 and 91.6kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Aug-91 (-6)	142.3
27-Aug-91 (7)	230.6
02-Sept-91 (13)	221.6
09-Sept-91 (20)	129.7
16-Sept-91 (27)	252.2
23-Sept-91 (34)	136.9
30-Sept-91 (41)	149.5

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0020/0005 Seroquel

This patient is a 44-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 25-July-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received benzodiazepines (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 5. The patient's weight was 75.2kg on Day 0 and 77.5kg on Day 27.

During treatment adverse events of probably related moderate headache and possibly related moderate agitation were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
24-July-92 (-1)	234.2
31-July-92 (6)	257.6

07-Aug-92 (13)	322.5
13-Aug-92 (19)	264.8
20-Aug-92 (26)	226.9
24-Aug-92 (30)	-

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 27. The reason for discontinuation was reported as 'refused to continue'

204636/0008/0026/0001 Seroquel

This patient is a 38-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 13-May-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 500mg/day by Day 9. The patient's weight was 79.0kg on Day 0 and 78.0kg on Day 41.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
30-Apr-92 (-13)	118.9
20-May-92 (7)	100.9
09-Jun-92 (27)	198.2
16-Jun-92 (34)	205.3
23-Jun-92 (41)	172.9

The patient discontinued Seroquel therapy at a dose of 500mg/day on Day 41. The reason for discontinuation was reported as 'completed study'.

204636/0008/0026/0006 Placebo

This patient is a 41-year old white female presenting with paranoid schizophrenia who began the trial on 14-July-1992 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel placebo. The patient's weight was 110.0kg on Day 0 and 115.0kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Jul-92 (0)	142.3
21-Jul-92 (7)	167.5
28-Jul-92 (14)	223.4
04-Aug-92 (21)	120.7
11-Aug-92 (28)	207.2
18-Aug-92 (35)	219.8
25-Aug-92 (42)	223.4

The patient discontinued on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0028/0110 Seroquel

This patient is a 36-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 08-Nov-1991 (Day 0). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. During the trial the patient was dosed Seroquel up to a level of 250mg/day by Day 4. The patient's weight was 75.5kg on Day 0 and 74.6kg on Day 42.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Nov-91 (-4)	160
14-Nov-91 (6)	154
22-Nov-91 (14)	137
29-Nov-91 (21)	131
06-Dec-91 (28)	218

13-Dec-91 (35)	158
20-Dec-91 (42)	148

The patient discontinued Seroquel therapy at a dose of 250mg/day on Day 42. The reason for discontinuation was reported as 'completed study'.

204636/0008/0031/0403 Seroquel

This patient is a 36-year old black female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 10-Mar-1992 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. She received chloral hydrate (sleep) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 11. The patient's weight was 76.8kg on Day 0 and 77.3kg on Day 22.

During treatment an adverse event of possibly related mild dizziness was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
06-Mar-92 (-4)	103
17-Mar-92 (7)	155
24-Mar-92 (14)	190
01-Apr-92 (22)	228

The patient discontinued Seroquel therapy at a dose of 550mg/day on Day 22. The reason for discontinuation was reported as 'lack of efficacy'.

5077IL/0004/0001/0008 Seroquel

This patient is a 40-year old black male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 09-Jan-1990 (Day 0).). No pre-trial medical history or treatment was recorded for this patient. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 200mg/day by Day 12. The patient's weight was 83.6kg on Day 0 and 90.9kg on Day 20.

During treatment adverse events of elevated SGPT, sedation, headache and tachycardia were reported, these were all reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
04-Jan-90 (-5)	74
09-Jan-90 (0)	106.3
13-Jan-90 (4)	259.4
17-Jan-90 (8)	122.5
21-Jan-90 (12)	104.5
25-Jan-90 (16)	113.5
29-Jan-90 (20)	111.7

The patient discontinued Seroquel therapy at a dose of 150mg/day on Day 20. The reason for discontinuation was reported as 'completed study'.

5077IL/0006/0001/0114 Seroquel

This patient is a 58-year old black male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 07-Jan-1992 (Day 0). He had a pre-trial medical history of eczema, fungal infection, hypertension, hepatomegaly, scrotal mass, perianal fissures, dementia, cataracts, schizophrenia, bipolar disorder and tardive dyskinesia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation) during the trial. During the trial the patient was dosed Seroquel up to a level of 750mg/day by Day 27. The patient's weight was 61.4kg on Day 0 and 61.4kg on Day 34 and his height was recorded as 175 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
03-Jan-92 (-4)	97
13-Jan-92 (6)	95
20-Jan-92 (13)	115

27-Jan-92 (20)	73
03-Feb-92 (27)	62
10-Feb-92 (34)	215

The patient discontinued Seroquel therapy at a dose of 750mg/day on Day 34. The reason for discontinuation was not recorded.

5077IL/0006/0011/1110 Seroquel

This patient is a 48-year old white male presenting with paranoid schizophrenia who began Seroquel at a dose of 25mg/day on 19-Mar-1992 (Day 0). He had a pre-trial medical history of tardive dyskinesia and schizophrenia. Pre-trial antipsychotic medication was not recorded. He received chloral hydrate (agitation, insomnia) during the trial. During the trial the patient was dosed Seroquel up to a level of 600mg/day by Day 29. The patient's weight was 82.5kg on Day 0 and 86.8kg on Day 41 and his height was recorded as 173 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Mar-92 (-2)	133
25-Mar-92 (6)	157
01-Apr-92 (13)	186
08-Apr-92 (20)	193
15-Apr-92 (27)	210
22-Apr-92 (34)	164
29-Apr-92 (41)	158

The patient discontinued Seroquel therapy at a dose of 400mg/day on Day 41. The reason for discontinuation was reported as 'completed study'

5077IL/0015/0012/1205 Haloperidol

This patient is a 34-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 18-Feb-1994 (Day 0). He had a pre-trial medical history of bronchitis, hyperglycemia, and alcohol and drug abuse. Pre-trial the patient received haloperidol for schizophrenia, this was stopped on 17-Feb-1994 (Day -1). He received the following concomitant medication during the trial: cogentin (EPS prophylaxsis), diabeta (hyperglycemia), hydrocodone, iodine, aspirin (left foot pain, body aches), prozac (unknown), contac (nasal congestion), 4-way nasal spray (nasal congestion), sinutab (sinus headaches), orudis (groin pain), flexeril, voltaren (left sciatic pain) and erythromycin (sore throat). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 6. The patient's weight was 136.4kg on Day 0 and 130.5kg on Day 357 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the study were as follows:

Date (day)	Glucose mg/dl
17-Feb-94 (-1)	268
04-Aug-94 (167)	516
16-Feb-95 (357)	328

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0013/1309 Seroquel

This patient is a 43-year old hispanic female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 18-May-1994 (Day 0). She had a pre-trial medical history of head injury, anemia, hepatitis, hypothyroidism, substance abuse and pollen allergies. Pre-trial the patient received trifluoperazine for schizophrenia, this was stopped on 17-May-1994 (Day -1). She received the following concomitant medication during the trial: propanolol (akathisia , anxiety), cogentin (EPS), triphosil-28 (oral contraceptive), chloral hydrate (anxiety), lorazepam (agitation), chlortrimetan (sinus congestion), flu shot (flu prevention), ibuprofen and tylenol (intermittent back/neck pain) During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 106.4kg on Day 0 and 99.1kg on Day 358 and her height was recorded as 168 cm.

During treatment an adverse event of increased sedation was reported, this was reported as mild and possibly related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-May-94 (-9)	254
31-Oct-94 (166)	250
14-May-95 (358)	122

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 358. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0019/1903 Seroquel

This patient is a 46-year old white female presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 23-Nov-1993 (Day 0). She had a pre-trial medical history of headaches, non insulin dependent diabetes and obesity. Pre-trial the patient received tiotixene for schizophrenia, this was stopped on 22-Nov-1993 (Day -1). She received the following concomitant medication during the trial: diabeta (non insulin dependent diabetes), lorazepam (agitation), lorcet plus, tylenol (headaches), tavist-D (nasal congestion), cataflam, oruvail and flexeril (back pain). The patient was dosed Seroquel at a level of 75mg/day throughout the trial. The patient's weight was 109.5kg on Day 0 and 109.5kg on Day 357 and her height was recorded as 168 cm.

During treatment adverse events of intermittent insomnia and constipation were reported, these were reported as mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
09-Nov-93 (-12)	245
10-May-94 (168)	313
15-Nov-94 (357)	434

The patient discontinued Seroquel therapy at a dose of 75mg/day on Day 357. The reason for discontinuation was reported as 'completed protocol'.

5077IL/0015/0021/2105 Haloperidol

This patient is a 63 year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 21-Dec-1993 (Day 0). He had a pre-trial medical history of

rash, hypertension, benign prostatic hypertrophy, shortness of breath and untreated elevated blood sugar. Pre-trial the patient received perphenazine for psychosis, this was stopped on 20-Dec-1993 (Day -1). He received the following concomitant medication during the trial: benadryl, chloral hydrate (insomnia) and lorazepam (agitation). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 9. The patient's weight was 109.1kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment an adverse event of probably related mild sedation was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
13-Dec-93 (-8)	327
03-Jan-94 (13)	282

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 15. The reason for discontinuation was reported as 'refused to continue'

5077IL/0015/0023/2310 Seroquel

This patient is a 43-year old male of 'other' ethnic origin presenting with paranoid schizophrenia who began Seroquel at a dose of 75mg/day on 02-July-1994 (Day 0). He had a pre-trial medical history of sinus bradycardia, mild peptic ulcer and stable insulin dependent diabetes. Pre-trial the patient received chlorpromazine for psychosis, this was stopped on 24-Jun-1994 (Day -8). He received insulin NPH (diabetes) during the trial. During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 3. The patient's weight was 58.6kg on Day 0 but was not measured at the end of the trial, his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
17-Jun-94 (-15)	363
30-Aug-94 (59)	406

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 59. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0026/2607 Seroquel

This patient is a 52-year old asian male presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 15-Dec-1993 (Day 0). He had a pre-trial medical history of myocardial infarction and increased cholesterol. Pre-trial the patient received perphenazine for psychosis, this was stopped on 14-Dec-1993 (Day -1). He received the following concomitant medication during the trial: lorazepam (agitation), lithobid (adjunct Tx schizophrenia), temazepam, chloral hydrate (insomnia), aspirin (heart condition) and mevacor (hypercholesterolemia). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 8. The patient's weight was 79.5kg on Day 0 and 79.3kg on Day 12 and his height was recorded as 168 cm.

During treatment no serious or attributable adverse events were reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
14-Dec-93 (-1)	192
28-Dec-93 (13)	240

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 12. The reason for discontinuation was reported as 'lack of efficacy'

5077IL/0015/0034/3411 Seroquel

This patient is a 41-year old black female presenting with undifferentiated schizophrenia who began Seroquel at a dose of 75mg/day on 14-Oct-1994 (Day 0). She had a pre-trial medical history of tubal ligation, substance abuse and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Oct-1994 (Day -1). She received the following concomitant medication during the trial: benzatropine (EPS prophylaxsis), desipramine (depression) and micronase (diabetes). During the trial the patient was dosed Seroquel up to a level of 300mg/day by Day 6. The patient's weight was 101.4kg on Day 0 and 122.7kg on Day 209 and her height was recorded as 168 cm.

During treatment an adverse event of mild dizziness was reported, this was mild and probably related. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl

05-Oct-94 (-9)	186
21-Apr-95 (168)	259

The patient discontinued Seroquel therapy at a dose of 300mg/day on Day 209. The reason for discontinuation was reported as 'completed study'.

5077IL/0015/0035/3502 Haloperidol

This patient is a 43-year old white male presenting with undifferentiated schizophrenia who began haloperidol at a dose of 2mg/day on 14-Mar-1994 (Day 0). He had a pre-trial medical history of depressed hypertension, elevated liver enzymes and diabetes. Pre-trial the patient received tiotixene for psychosis, this was stopped on 13-Mar-1994 (Day -1) . He received the following concomitant medication during the trial: lorazepam (agitation), lithium, nortriptyline (depression), glucotrol (diabetes), accupril (hypertension), ativan (increased anxiety), vantin (URI), tylenol, motrin (headache), chloral hydrate (insomnia), alcaine, cyclogyl, mydfrin, profenal, BSS, dexamethasone, garamycin and viscoat (cataract surgery). During the trial the patient was dosed haloperidol up to a level of 12mg/day by Day 5. The patient's weight was 108.2kg on Day 0 and 106.8kg on Day 364 and his height was recorded as 168 cm.

During treatment an adverse event of serious cataract surgery, unrelated to trial therapy, was reported. The patient's blood glucose levels during the trial were as follows:

Date (day)	Glucose mg/dl
08-Mar-94 (-6)	191
30-Aug-94 (169)	364
13-Mar-95 (364)	209

The patient discontinued haloperidol therapy at a dose of 12mg/day on Day 364. The reason for discontinuation was reported as 'completed protocol'.

APPENDIX B

Patient narratives: postmarketing data

Cases of new-onset diabetes mellitus

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose levels

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 13.6 kg. Fasting blood sugar showed glucose level over 700 mg/dl. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

2000UW00266 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 12-year old male patient who had been receiving Seroquel 300mg daily since 06 Dec 1999. On 26 Jan 2000, the patient experienced hyperglycemia (blood sugar level of 863) and was hospitalized. Seroquel was discontinued and the patient was treated with insulin. His blood sugar level has decreased to 170 mg/dl. Concomitant medications include Zoloft, Klonopin, Haldol and depakote.

Follow-up 23 Feb 2000: Pharm D reports that "after further testing, the attending physicians did not feel that Seroquel was involved in the patient's hyperglycemia. The patient was diagnosed with insulin dependent diabetes mellitus. The patient is currently being seen in the diabetic clinic."

1999UW03532 Seroquel

Diabetes mellitus, weight gain

A report has been received from a physician concerning a 45-year old female who has been receiving Seroquel and developed diabetes. Physician feels that Seroquel may possibly be responsible for the development of diabetes.

Follow-up 11 Nov 1999: Physician reports that the 47 year old female (not 45) had been receiving Seroquel 600mg daily for schizoaffective disorder for a total of 12 months and experienced a severe 50 pound weight gain (date of onset unknown with no improvement). The patient was hospitalized in June 1999 due to the development of severe diabetes mellitus (difficult to control hyperglycemic). The patient is now receiving insulin and although the event continues it has improved. Seroquel was tapered for discontinuation. Concomitant medications include Klonopin and Benadryl. The patient has a medical history of Hepatitis C, hypertension and arthritis. Physician states that he believes "Seroquel caused the weight gain which brought out diabetes in this patient likely predisposed for this condition."

1999UW03387 Seroquel

Type II diabetes, drowsiness

A report has been received from a physician concerning a 17-year old Hispanic male patient who had been receiving Seroquel 100 mg every evening since Jan 1999 for psychotic depression and auditory hallucinations. In March 1999, due to drowsiness in the daytime the dosage of Seroquel was decreased to 50mg every evening. In July 1999, the patient was diagnosed with Type II diabetes. On 11 Sept 1999, Seroquel dosage was again decreased to 25mg every evening. The patient had been receiving Risperidol prior to Seroquel. Concomitant medications include Ritalin for attention disorder and Serzone for depression.

1999UW00969 Seroquel

Complications of diabetes mellitus

A report has been received from a physician concerning a 28-year old male patient who was taking Seroquel and Lithium (doses, duration, indications unknown). The patient presented to the emergency room following flu-like symptoms lasting for one week, as well as asthma, and weakness in the legs. There was no report of increase or decrease in body temperature before presentation. His temperature at the emergency room was 107+ F (rectal probe 108 F), cardiac arrhythmias, liver enzymes were twice normal, blood glucose was 2240 mg/dl, potassium low, CPK normal, lithium level was not elevated (0.4 or 0.6 mEq/L). The patient developed severe arrhythmias, ventricular fibrillation, and disseminated intravascular coagulation with low fibrinogen. He died at 4:00 a.m., on REDACTED The tentative diagnosis is neuroleptic malignant syndrome. Complete autopsy reports are pending. Follow-up has been requested.

*Follow-up received 22-Mar-1999: A pharmacist reports that the patient started Zithromax on 10-Mar-1999, to counter a suspected infection. She also reports that the patient had been bleeding from his eyes and nose.

*Follow-up received 14-Mar-1999: The patient presented on 14-Mar-1999 with focal twitching. He had increased tone, no dolls eyes or corneal responses. The pupils were mid-position and not reactive, and there was no reaction to noxious stimuli.

Ativan was started, to a loading dose of 0.03 mg/kg. No further seizure activity was noted. The patient was started on Dantrium 2 mg/kg, with the dose of 150 mg. The patient developed cardiac arrhythmia requiring anti-arrhythmics. He continued to be acidotic and received bicarbonate and insulin. Split fibrins were ordered for the bleeding abnormalities, as well as whole blood. A pacemaker was placed and a rhythm obtained. The patient had been packed in ice from the onset. He died on REDACTED The reporter attributed the event to a drug effect from multiple prescriptions.

*Follow-up received 05-May-1999: The county coroner reported the patient's cause of death as complications of diabetes mellitus. The patient did not have neuroleptic malignant syndrome. There had been a history of a 4.5 to 7.3 kg weight loss with flu-like symptoms, and blood glucose of 123.8 mg/dl on admission.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel fumarate 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 months after starting Seroquel fumarate, the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

1999AP05218 Seroquel

Diabetes during pregnancy

No further information available.

1999AP02989 Seroquel

Diabetes mellitus

This patient started treatment with Seroquel on 13 Nov 1998 and with fluoxetine on 12 Nov 1998. Urine and blood tests on 26 Nov 1998 indicated that she had developed diabetes mellitus. Urinary sugar was raised and blood sugar was 308 mg/dl.

1998UW48512 Seroquel

Diabetes mellitus

A report has been received from a pharmacist concerning a 42-year-old male patient who has taken Seroquel since July 1998. On 31 Aug 98 he was diagnosed with diabetes mellitus. Further information is being requested.

*Follow up 12 Oct 99: Further information reveals that the patient was receiving Seroquel 200 mg for a bipolar disorder since July 1998. On 31 Aug 98, patient was admitted to the hospital with a new-onset diabetes mellitus. Patient had no prior history of glucose intolerance or hyperglycemia. Four months prior to admission blood glucose was 126 mg/dl and 107 mg/dl. At admission blood glucose was 607 mg/dl. Seroquel was tapered, then discontinued. Insulin requirements decreased markedly and insulin was eventually discontinued in January 1999. Patient was also receiving lithium carbonate, gabapentin, clonazepam, and venlafaxine.

This patient's details have been published in a literature case report (Sobel, Jaggers and Franz, 1999).

1999AP01985 Seroquel

Non-insulin dependent diabetes

Terse Narrative: Concomitant medication includes cyproterone acetate which can influence carbohydrate metabolism.

1998UW48844 Seroquel

Hyperglycemia, diabetes

A report has been received from a physician concerning a male patient in his early forties who has been receiving Seroquel for 4 weeks and is experiencing hyperglycemia and diabetes. The patient, who has no previous history of diabetes, is now showing blood sugars of over 600 mg/dl. Follow-up will be requested.

1999UW00967 Seroquel

Diabetes

A report has been received from a physician concerning a 17-year old male who is receiving Seroquel 200mg twice daily for schizophrenia. The patient was initially started on 100mg which was increased. While being hospitalized for his schizophrenia, routine lab work revealed diabetes which is being treated with glucotrol 300mg daily. Patient also receives Paxil and Depakote. Patient continues on Seroquel.

Cases of diabetic ketoacidosis

1998UW49554 Seroquel

Cerebrovascular accident, diabetic acidosis, transient ischemic attack, collapse

A report has been received from a physician concerning a 58-year old male patient who received Seroquel 800 mg daily for schizoaffective disorder. The patient has a history of diabetes and cerebrovascular accident. He also takes gabapentin. The patient experienced a transient ischemic attack and was unresponsive except for painful stimuli. Five minutes later, the patient recovered fully. The following day, he collapsed in the shower and died. An autopsy was performed and the primary cause of death was listed as diabetic acidosis and secondary to cerebrovascular accident. Additional information will be requested.

2000UW01164 Seroquel

Ketoacidosis, diabetes mellitus, polyuria, polydipsia, weight loss, elevated glucose level

A report has been received from a registered pharmacist, via sales rep, concerning a 43-year old male with a history of mental illness who started Seroquel 200mg HS in December 1999. Over a period of a few weeks he developed polyuria, polydipsia, and an unexplained weight loss of over 30 lbs. Fasting blood sugar showed glucose level over 700. Patient developed ketoacidosis and was hospitalized where a diagnosis of new onset diabetes mellitus was made. (Patient has no family history of diabetes). Patient is also receiving "fenlafaxin" (venlafaxine) and continues on Seroquel. More information will be sought.

1999AP05757 Seroquel

Diabetes, ketoacidosis

A report has been received from a physician concerning a 25-year old male patient who has been receiving Seroquel 750mg daily for psychosis since November 1997. He was receiving acamprosate, Depixol and Priadel concomitantly.

In August 1999, 1 year 9 months after starting Seroquel, the patient was hospitalized due to the development of diabetes mellitus and ketoacidosis. It was also reported that he had experienced

weight gain (date of onset and quantity of weight gained unknown). The patient is now being treated with insulin, has recovered with residual effects and Seroquel is continuing.

The reporter had no opinion regarding the causal relationship between the events and Seroquel, but commented that the weight gain may have been a contributing factor.

Weight gain is listed in the core prescribing information for Seroquel.

Cases of hyperglycemia

2000UW01047 Seroquel

Cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, excitable, difficulty in waking, negative mood, decreased sex drive, inability to have orgasms

A report has been received from a nutritionist, who is also the patient, who has been receiving Seroquel, six 25 mg tablets at night, since September 1997 for psychotic episodes. She has been experiencing cough, elevated cholesterol, weight gain, constipation, asthma, worsening fibromyalgia, muscle spasms in her neck and back, tenseness in neck, urine odor, worsening arthritis, worsening endometriosis, elevated blood sugar, she is more excitable, has difficulty in waking, negative mood, decreased sex drive, and inability to have orgasms.

1998AP50408 Seroquel

Hyperglycemia (non-serious)

Pharmacist considers hyperglycemia unrelated to Seroquel, however patient's nurse considers the event related.

APPENDIX C

The effect of Seroquel on weight gain

Source material

The weight information provided below has been taken from the interim assessment of Seroquel Trial 5077IL/0051 (an open label extension [OLE] trial; data cut-off date March 28 2000).

Trial 5077IL/0051 is an international, multicentre, open-label extension of treatment with Seroquel for schizophrenic patients who have participated in the Seroquel Phase IIIb clinical trial program (namely Trials 0050, 0052, 0053 and 0054).

Open treatment with Seroquel began, in most cases, with an initial dose-titration period during which the dose was increased according to the patient's clinical condition. Thereafter, Seroquel dosing was flexible, up to a maximum of 800 mg/day, administered twice daily.

Weight data for the analyses are taken from patients who were exposed to Seroquel either during randomized treatment in the feeder trial or open-label Seroquel treatment during OLE.

Analyses

To observe the effect of Seroquel monotherapy on weight gain, the following analyses were undertaken:

- **The effect of Seroquel monotherapy on weight over time (between 1 and 1.5 years)**
  - in patients with weight data *both* at baseline and at 1 specific timepoint during treatment with Seroquel monotherapy: Weeks 53-78

  If a patient had more than 1 visit within each timepoint, then the mean value was taken.

- **The effect of Seroquel monotherapy on weight across the dose range**
  - in patients with weight data at baseline and endpoint

  Data were classified into the following 3 dose ranges (according to the patient's dose of Seroquel at endpoint): ≤ 300 mg, > 300 mg to ≤ 500 mg, > 500 mg. (It should be noted that time on treatment for each patient in this cohort will vary).

Results

In patients with weight data both at baseline and at 1 specific timepoint during Seroquel monotherapy treatment (between 1 and 1.5 years), the mean weight change was 1.87 kg and the median weight change was 1.20 kg (Tables C1 and C2).

Weight change observed at the end of treatment with Seroquel monotherapy was consistent across the dose range (Tables C3 and C4).

Table C1 Patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel	
	Weeks 1-4 (n=130)	Weeks 53-78 (n=130)
Mean weight (kg)	72.57	74.44
Median weight (kg)	70.25	72.00
SD	15.50	15.59
Min	43.0	45.6
Max	128.7	136.0

Table C2 Change from first dose of Seroquel in patient weight (same patients at each timepoint): Seroquel controlled and open label data

Seroquel controlled and open label	Timepoint from first dose of Seroquel
	Weeks 53-78 (n=130)
Mean weight change (kg)	1.87
Median weight change (kg)	1.20
SD	7.63
Min	-27.2
Max	25.5

Table C3 Patient absolute weight at baseline and endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Baseline				
Mean weight (kg)	75.88	73.91	73.10	74.37
Median weight (kg)	73.40	71.75	69.70	71.50
SD	16.13	17.08	15.10	14.83
Min	47.5	43.0	50.2	46.2
Max	128.0	146.0	130.0	126.0
Endpoint				
Mean weight (kg)	77.10	74.66	73.30	74.04
Median weight (kg)	75.00	72.00	72.50	72.00
SD	15.69	19.30	16.52	15.52
Min	45.0	46.0	45.8	43.9
Max	128.5	172.8	140.0	135.0

Table C4 Change in weight from baseline to endpoint across dose: Seroquel controlled and open label data

Seroquel controlled and open label	Modal dose of Seroquel at endpoint			
	No dose recorded (n=103)	< 300 mg (n=72)	> 300 mg to ≤ 500 mg (n=71)	> 500 mg (n=134)
Mean weight change (kg)	1.21	0.75	0.20	-0.34
Median weight change (kg)	1.00	-0.25	-0.60	0.00
SD	7.33	7.25	7.86	7.91
Min	-21.8	-14.5	-21.4	-27.2
Max	26.5	26.8	27.3	23.0
N	103	72	71	134

Summary

The effect of Seroquel on weight change in the long-term is minimal. There does not appear to be any relationship between weight change and the dose of Seroquel.

APPENDIX D

Correspondence with regulatory agencies

APPLICATION FOR MARKETING AUTHORIZATION
-MR PROCEDURE

Seroquel (REF No NL/H/156/01-03)
Quetiapine Zeneca (Ref No NL/H/157/01-03)

Consolidates Response to Concerned Member States

November 1999

COUNTRY : SPAIN SPC Question number ES-7:

According to SPC, quetiapine was associated with weight gain predominantly during the early weeks of treatment but the results of controlled and uncontrolled trials showed a duration-related increase in the incidence of clinically significant weight increase. This issue should be clarified.

AstraZencea response:

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

The apparent inconsistency identified by the reviewer is driven by 2 distinct factors. Firstly, the 2 columns in Table 59 in the Clinical Data Summary (number [%] with >7% the baseline weight and total mean weight increase [kg], respectively) are not directly comparable. The total mean weight increases have been calculated using the *last value* for each patient within each time period. (These mean weight change also takes into account patients who lose weight). The other column, however, reports all patients who exceeded the 7% threshold *at any time* during the time period, including transient effects.

In order to clarify the situation, Table 7 presents the percentage of patients who experienced either a >7% weight increase or a >7% weight reduction by treatment duration(using an LVCF approach within each time period). In addition, the mean weight change by treatment duration is presented. (The data in Table 1 are based on the original data presented in the dossier).

Table 1 Weight data in patients treated with quetiapine in the Phase II/III controlled and uncontrolled trials

Treatment duration	N	% of patients			Mean weight change (kg)
		>7% reduction in weight	No significant change in weight	>7% gain in weight	
5 to 6 weeks	778	3.7	74.8	21.5	2.08
6 months	1190	12.0	62.9	25.0	0.76
12 months	573	13.8	50.9	35.3	1.59
>12 months	346	16.8	42.7	40.4	2.00

As can be seen in Table 7, at week 6 there is a marked imbalance between the percentage of patients who have experienced a >7% weight increase and reduction. This reflects the pharmacological effect of quetiapine. However, after this short-term effect, the increases in each category are more balanced reflecting the natural variability of weight across time.

Zeneca believes that the current label accurately reflects the pharmacological effect of quetiapine, in that it is associated with weight gain predominantly during the early weeks of treatment.

APPLICATION FOR MARKETING AUTHORISATION

Response to comments made by the French Medicines Agency (FMA) in Annexe B of their letter dated 9 April 1998

June 1999

The uncertainty regarding the efficacy should be balanced with the undesirable effects, ie, hepatocytolysis (ALT > 5 x ULN in 0.4% of subjects), opacities on the lens, weight gain in 15% to 20% of subjects (2.8 kg in 6 months and 5 kg after 6 months) and neutropenia (4 to 5 per 1000).

AstraZeneca response (to weight gain):

The Commission commented that between 15% and 20% of patients had an increase in body weight of >7%. Table 6-8 provides data from the updated safety database.

Table 6-8 Magnitude of effect over time of quetiapine on weight gain in the Phase-II/III trials

Duration of exposure	Controlled trials (Mean duration 48.1 days)		Controlled and uncontrolled trials (Mean duration 164.4 days)	
	Number (%) with >7% the baseline weight	Total mean weight increase (kg)	Number (%) with >7% the baseline weight	Total mean weight increase (kg)
≤1 week	11 of 396 (2.8)	0.39	15 of 564 (2.7)	0.15
>1 to 2 weeks	38 of 475 (8.0)	0.67	45 of 661 (6.8)	0.64
>2 to 3 weeks	50 of 350 (14.3)	1.54	60 of 475 (12.6)	1.08
>3 to 4 weeks	48 of 338 (14.2)	1.65	62 of 495 (12.5)	1.20
>4 to 5 weeks	50 of 236 (21.2)	2.31	53 of 308 (17.2)	1.66
>5 to 6 weeks	164 of 727 (22.6)	2.19	167 of 778 (21.5)	2.08
>6 weeks to 6 months	61 of 289 (21.1)	1.55	337 of 1190 (28.3)	0.76
>6 to 12 months	34 of 66 (51.5)	5.15	229 of 573 (40.0)	1.59
>12 months	4 of 8 (50.0)	5.30	180 of 346 (52.0)	2.00
At any time	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

There was a duration-related increase in the incidence of clinically significant weight gain (>7% of baseline) in patients treated with quetiapine. The number of patients treated with quetiapine in the controlled and uncontrolled Phase-II/III trials who had an increase in body weight of >7% of baseline at any time during treatment (610 of 2216 [27.5%]) was higher than that at the end of

treatment (430 of 2216 [19.4%]), indicating that patients who had put on weight could subsequently lose it on continued quetiapine therapy.

The Commission commented that weight gain was 2.8 kg in the first 6 months and 5 kg after 6 months. Data from the updated safety database indicate that the mean greatest weight increase was 5 to 6 kg, and was higher in patients treated with quetiapine in the controlled trials compared with those in the combined controlled and uncontrolled trials. It should be noted that the number of patients in the controlled trials at the later time points is small, thus making it difficult to assess whether the increase in weight continues at the same rate or whether it slows after about 6 months.

Table 6-9 shows the mean weight increase and the incidence of clinically significant weight increases (>7% of baseline) by dose of quetiapine in the updated safety database.

Table 6-9 Number (%) of patients with clinically significant increase in body weight (>7% of baseline) by dose of quetiapine in the Phase-II/III trials

Dose of quetiapine	Controlled trials (Mean dose 342.3mg/day)		Controlled and uncontrolled trials (Mean dose 377.4mg/day)	
(mg/day)	Number (%) with >7% the baseline weight	Mean weight increase (kg)	Number (%) with >7% the baseline weight	Mean weight increase (kg)
<150	43 of 352 (12.2)	0.39	34 of 298 (11.4)	-0.18
≥150 but <300	51 of 276 (18.5)	1.51	129 of 466 (27.7)	1.37
≥300 but <450	95 of 498 (19.1)	1.49	169 of 623 (27.1)	1.30
≥450	106 of 422 (25.1)	2.23	274 of 822 (33.3)	0.09
Any dose	295 of 1548 (19.1)	1.45	610 of 2216 (27.5)	0.66

The mean weight change in patients in each group was small, although there was some evidence of a dose-related increase in incidence of patients gaining >7% of baseline in body weight.

In summary, these additional data confirm the findings in the original MAA and are consistent with the wording in the Summary of Product Characteristics, which states that treatment with quetiapine is sometimes associated with increases in body weight.

Response to the letter from the IKS (Interkantonale Kontrollstelle fur Heilmittel) dated 17 April 1997 concerning quetiapine tablets 25, 100 and 200 mg

September 1998

5 **The level of weight gain (22% of patients gained more than 7% in weight) was clearly higher than that observed for the standard preparation haloperidol. Sedation and autonomic, anticholinergic effects were more frequent than with the reference preparation. Where investigated, there was also a clear increase in serum cholesterol levels.**

5.1 Effect of quetiapine on weight gain

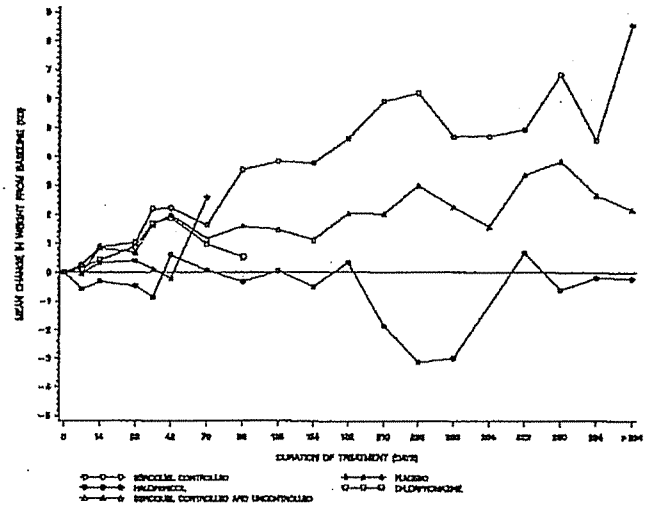
Supporting data are provided in the Supporting Documentation on the Safety of Quetiapine, Section 1.7.

As with most other antipsychotic agents - including recently approved agents such as olanzapine and risperidone - quetiapine was associated with weight gain.

The incidence of adverse events of weight gain in patients treated with quetiapine in the placebo-controlled trials was small (2.0% of 510) and lower than that in patients treated with olanzapine in similarly designed placebo-controlled trials (5.6% of 248). Patients treated with quetiapine in the placebo-controlled trials gained a mean of approximately 2 kg body weight, similar to that observed with olanzapine (2.8 kg; US Summary Basis of Approval for olanzapine).

The incidence of clinically significant weight increase (>7% of baseline) in patients treated with quetiapine in the Phase-II/III trials increased with time, suggesting that weight gain may be a manifestation of successful long-term treatment with quetiapine. Figure 2 shows the mean change in body weight over time in the Phase-II/III controlled and uncontrolled clinical trials.

Figure 2 Mean change in body weight by duration of therapy in the Phase-II/III trials



The proportion of patients who gained >7% body weight during quetiapine therapy appeared to increase with increasing dose; this may have been because patients tended to take high doses of quetiapine for longer periods than low doses.

The present wording in the section on 'Possible adverse reactions' in the Quetiapine SmPC adequately alerts the prescriber to the above findings in the clinical trials programme for quetiapine.

REPLY TO INSTRUCTIONS FROM IST MHW EVALUATION CENTRE (EC) HEARING

Seroquel 25/100 mg tablets

March 1999

Instruction 82

Make comments on a possible mechanism of hyperplasia of the glucagon-secreting cells in the pancreas and clinical relevance of this finding.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson et al 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate. In addition, the plasma prolactin levels did not increase in clinical studies. Therefore, the risk for human could be low.

References

Sorenson et al. Endocrinology 1995; 136: 4092-8.

Weinhaus et al. Endocrinology 1996; 137: 1640-9.

APPLICATION FOR MARKETING AUTHORISATION APPROVAL IN SWEDEN

Response to the Medical Products Agency's (MPA's) Assessment Report of 27 January 1997 concerning quetiapine (SEROQUEL™) tablets 25, 100 and 200 mg (Aspnr: 96-243, 96-244, 96-245)

February 1997

The mechanism of the hyperplasia of the glucagon secreting cells in the pancreas in the 1-year rat study should be discussed.

AstraZeneca response:

Hyperplasia of small glucagon secreting cells (α cells) at the periphery of pancreatic islets was seen in the 75- and 250-mg/kg/day groups after administration of quetiapine for 12 months; this was minimal in severity and was not present after administration for 2 years at the same dose levels. Indeed, the incidences of islet hyperplasia and islet cell tumours were comparable across the dose groups at 2 years, and the common, spontaneous, age-related degenerative change of irregularly shaped islets was reduced in incidence.

Glucagon has a glycogenolytic action in the liver that results in an elevated blood glucose. As no significant changes in blood glucose were seen it seems unlikely that the histological changes were reflected in a functional disturbance.

Lactogenic hormones, including prolactin, are important regulators of insulin secretion and islet β cell proliferation (Sorenson and Stout 1995, Weinhaus et al 1996). The function of pancreatic islet α and β cells is co-ordinated and mutually responsive. It is possible that stimulation of β cell function by prolactin following administration of quetiapine resulted in a concurrent change in α cell homeostasis. This change, occurring in an environment of substantial hormonal disturbance, did not persist on continued dosing and showed no clear functional correlate.

EXHIBIT 27

Unknown

From: Geller, Wayne
Sent: Wednesday, December 05, 2001 1:01 PM
To: Patridge, Melissa
Subject: RE: Metabolic issues

Thanks a lot Melissa

-----Original Message-----
From: Patridge, Melissa
Sent: Wednesday, December 05, 2001 12:46 PM
To: Geller, Wayne
Subject: RE: Metabolic issues

On December 4, 2001 a search was performed on ClinTrace for cumulative Seroquel reports of HLTs Diabetes mellitus (all forms) and Hyperglycaemic conditions NEC.

A total of 47 reports were noted. The earliest Sponsored study report was initially reported on April 5, 1994. There were eight reports including concomitant disease of diabetes. Of these, five reports were from spontaneous reporters, three were from sponsored studies and one was a literature report.

There were 39 reports that did not include reference to history of diabetes. Of these, eight were from sponsored studies, four from literature and the remaining were spontaneous reports.

-----Original Message-----
From: Geller, Wayne
Sent: Tuesday, December 04, 2001 1:48 PM
To: Patridge, Melissa
Subject: RE: Metabolic issues

M,

From the begining of history through November 30, 2001 please.

Thanks,
Wayne

-----Original Message-----
From: Patridge, Melissa
Sent: Tuesday, December 04, 2001 12:18 PM
To: Geller, Wayne
Subject: RE: Metabolic issues

Please clarify timeframes.

Marketed September 1997 and Clinical (date of first report)?

-----Original Message-----
From: Geller, Wayne
Sent: Tuesday, December 04, 2001 9:02 AM
To: Patridge, Melissa
Subject: FW: Metabolic issues

M.

Please do a BO search for the number of reports of Diabetes or hyperglycemia and provide me with just a number. Include both clinical and postmarketing timeframes.

Thanks,
Wayne

-----Original Message-----
From: Olbrich, Richard
Sent: Tuesday, December 04, 2001 3:35 AM
To: Hagger, Simon; 'carole.nadin@btinternet.com'; Geller, Wayne
Cc: Aked, Dominic M; Owen, Richard T; Ney, Christine A; Brecher, Martin; Lapp, Carrie
Subject: RE: Metabolic issues

Simon I agree with Wayne's proposal.

Wayne I'd like to be able to revise DOF 89 accordingly. Once you get the information from Carrie could you please let me know and send me DOF 89 with your suggested revisions.

Kind regards Richard

Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

-----Original Message-----
From: Hagger, Simon
Sent: Monday, 03 December, 2001 21:12
To: Olbrich, Richard; 'carole.nadin@btinternet.com'
Subject: FW: Metabolic issues

Hi both,
What do you think to Waynes suggestion below as a way forward? I'm happy with it if it can be worked out and done this way.
Thx
Simon

-----Original Message-----
From: Geller, Wayne
Sent: Monday, December 03, 2001 3:38 PM
To: Hagger, Simon
Subject: RE: Metabolic issues

Dear Simon,

My preference would be to provide incidence rates derived from comparative clinical trial data where the numerator and denominator are both known, and not estimates. If this is not possible, I would propose something similar to what Dom is proposing below, except it is important to understand that we are calculating a reporting rate which is far less accurate than (and can not be used in comparison to) a true incidence rate. Instead of providing reporting rates in absolute numbers, I would suggest using something similar to the CIOMS definitions:

Kind regards,
Wayne

-----Original Message-----
From: Hagger, Simon
Sent: Monday, December 03, 2001 3:09 PM
To: Geller, Wayne
Subject: FW: Metabolic issues

Hi Wayne,
please see Dominic Aked's response to my question over the metabolic data issue. Do either of the approcahes seem a reasonable compromise? I'd appreciate your thoughts.
Kind regards
Simon

-----Original Message-----
From: Aked, Dominic M
Sent: Thursday, November 29, 2001 5:28 AM
To: Hagger, Simon; Bowen, Rebecca
Cc: Owen, Richard T
Subject: RE: Metabolic issues

Hi Simon

I agree that presenting absolute figures will cause problems as they will need to be constantly updated.

We could consider presenting an estimate of the incidence, based on projected usage from sales. This might say something like.....

Post-marketing surveillance suggests the incidence of ??? glucose dyregulation associated with Seroquel is rare/infrequent (less that 0.??1%)

We would need to make assumptions about patient usage

Alternatively, we could stay with the data from placebo controlled trials.

Wayne's input is essential

Kind regards

Dom

-----Original Message-----
From: Hagger, Simon

Sent: Tuesday, 27 November, 2001 20:05
To: Aked, Dominic M; Bowen, Rebecca
Subject: FW: Metabolic issues

Dear Rebecca and Dom,
Please can you comment on the attached message from Wayne Geller concerning updating a DOF on metabolic issues from which we took data from post-marketing data from the FDA. How do you feel we should proceed bearing in mind Waynes comments? I would suggest we look at the impact of the DOF with this data removed.
Regards
Simon

-----Original Message-----
From: Geller, Wayne
Sent: Monday, November 26, 2001 11:13 AM
To: Olbrich, Richard; Hagger, Simon
Cc: Owen, Richard T
Subject: RE: Metabolic issues

Dear Richard and Simon,

The November 2000 discussion document on glucose dysregulation included the following numbers of events based on a data cut-off of October 2000:

"A search was conducted for all cases in which diabetes mellitus, hyperglycemia, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were reported with SEROQUEL. The following are narratives for these 28 cases".

The numbers provided here are out of date as there have been additional reports of DM and related maladies that have been received since October 2000. In addition, there has been considerable discussion of this in the literature. Caution should always be exercised in presenting any number of postmarketing adverse events as the number will increase over time and the number of events is likely to not represent the true number of events of that type due to underreporting and other biases. I am not keen on sharing numbers of postmarketing events and would suggest that you not do so either.

Kind regards,
Wayne

-----Original Message-----
From: Carole Nadin [mailto:carole.nadin@btinternet.com]
Sent: Thursday, November 22, 2001 12:01 PM
To: Olbrich, Richard; Hagger, Simon; Geller, Wayne
Cc: rob.kite@cmc.co.uk; X:Patefield, Iain (External)
Subject: Re: Metabolic issues

Attached.
Carole
----- Original Message -----
From: "Olbrich, Richard" <Richard.Olbrich@astrazeneca.com>
To: "'Carole Nadin'" <carole.nadin@btinternet.com>; "Hagger, Simon" <Simon.Hagger@astrazeneca.com>; "Geller, Wayne" <Wayne.Geller@astrazeneca.com>
Cc: <rob.kite@cmc.co.uk>; "X:Patefield, Iain (External)" <Iain.Patefield@CMC-international.com>
Sent: Thursday, November 22, 2001 3:34 PM
Subject: RE: Metabolic issues

Carole many thanks for your comments. Please resend the attachment as I've not received it. Wayne could you please comment on this. I enclose DOF 89 for your reference.

Kind regards Richard
Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

-----Original Message-----
From: Carole Nadin [mailto:carole.nadin@btinternet.com]
Sent: Wednesday, 21 November, 2001 16:17
To: Olbrich, Richard; Hagger, Simon
Cc: rob.kite@cmc.co.uk; X:Patefield, Iain (External)
Subject: Re: Metabolic issues

Dear Richard and Simon

This would be quite a significant change to the DoF and to the slides, as it more than doubles the number of spontaneous reports of diabetes. Would you mind double-checking it, please, before we change the slides and the DoF? The source of the data in DoF 89 was page 26 of the FDA response document (dated August 2000), which stated that there had been 12 reports of diabetes mellitus up to May 2000. This document was presumably quite thoroughly data-checked, and is also dated later than the presentation that Wayne Geller refers to (June 2000). As he said he did not know the source of the 12 cases figure, I attach a copy of the source document.
Could you ask him to confirm that the 12 cases figure is definitely wrong, please, and that it should definitely be replaced with his figure of 27 cases? Is it possible that there could be some difference in definition between the figure of 12 cases in the FDA document and the figure of 27 cases from Wayne Geller?
If it is confirmed that the figure in the DoF should be changed, could you also send me the relevant analysis that is the source of the 27 cases figure, please? Chip will need to sign off again, so I will need to tell him in the covering note what has changed and why.
Regards
Carole
----- Original Message -----
From: "Olbrich, Richard" <Richard.Olbrich@astrazeneca.com>
To: "Geller, Wayne" <Wayne.Geller@astrazeneca.com>;
<carole.nadin@btinternet.com>
Cc: "Owen, Richard T" <Richard.Owen@astrazeneca.com>; "Brecher, Martin"
<martin.brecher@astrazeneca.com>; "Ney, Christine A"
<christine.ney@astrazeneca.com>; "Rice, Moira M"
<Moira.Rice@astrazeneca.com>; "Hagger, Simon"
<Simon.Hagger@astrazeneca.com>; "Swalley, Jeffrey S"
<jeffrey.swalley@astrazeneca.com>; "Stening, Göran K"
<Goran.K.Stening@astrazeneca.com>; "Sayce, Rod" <Rod.Sayce@astrazeneca.com>;
"Dev, Vikram J" <vikram.dev@astrazeneca.com>; "Aked, Dominic M"

<Dominic.Aked@astrazeneca.com>
Sent: Tuesday, November 20, 2001 4:49 PM
Subject: RE: Metabolic issues

Wayne thanks for pointing this out.

Carole could you please amend DOF 89 to state 27 cases as opposed to 12 and also update the weight slide kit which also contains this incorrect information.

Kind regards Richard
Richard Olbrich PhD
Medical Affairs Manager- Seroquel
PS&L
AstraZeneca
Alderley House Alderley Park
Macclesfield Cheshire SK10 4TF
United Kingdom
Tel: +44 (0) 1625 515219
Fax: +44 (0) 1625 515682
Email richard.olbrich@astrazeneca.com

> -----Original Message-----
> From: Geller, Wayne
> Sent: Tuesday, 20 November, 2001 16:23
> To: Olbrich, Richard
> Cc: Owen, Richard T; Brecher, Martin; Ney, Christine A; Rice, Moira M;
> Hagger, Simon; Swalley, Jeffrey S; Stening, Göran K; Sayce, Rod; Dev,
> Vikram J
> Subject: RE: Metabolic issues
>
> Dear Richard et al,
>
> In response to your question below, I have not had an in depth look at
> either DM or hyperlipidemia recently. We have been tied-up with other
> issues and intend to have another look at these issues when we are able to
> do so. I do have a comment about the following statement which appears
> below (in this e-mail):
>
> Seroquel - extremely low incidence of diabetes
> mellitus
> (post-marketing data)
> * Approximately 623 000 patients received Seroquel between launch in
> the US (1997) and May 2000
> * Only 12 cases of diabetes mellitus reported
>
>
> This figure (12 reports of DM) is incorrect, and I don't know the source
> of this data. DM was presented at SERM in June 2000 with a data cut-off
> of May 2000. Through that time, there were 27 reports of diabetes
> mellitus and 2 reports of hyperglycemia received by AstraZeneca.
>
> Kind regards,
> Wayne
> -----Original Message-----
> From: Olbrich, Richard
> Sent: Tuesday, November 20, 2001 4:18 AM
> To: Sayce, Rod
> Cc: Owen, Richard T; Brecher, Martin; Geller, Wayne; Ney,

> Christine A; Rice, Moira M; Hagger, Simon; Swalley, Jeffrey S; Stening,
> Göran K
> Subject: RE: Metabolic issues
>
> Rod thanks for the note. Just to clarify I presume that you are
> suggesting that we publish on 'metabolic issues' which includes diabetes,
> weight and lipids? . We'd be defining metabolic issues as diabetes, weight
> and lipids - Martin do you agree?
>
> I agree that we would approach Goran's team to ask for the analysis.
>
> However before we do this I'd like to be clear as to exactly what we
> would want to 'claim' from the publication as this will drive Goran's
> analysis: for example do we want to say:
>
> 1. Seroquel is not associated with diabetes or its exacerbation.
> 'A review of the controlled clinical trials and the post marketing
> safety data base resulted in no statistically significant adverse effects
> of Seroquel with insulin levels, blood glucose leves or the incidence of
> diabetes.' (similar to DOF 89 and the reg defence document).
>
> 2. Seroquel does not adversely affect cholesterol, LDL,
> triglycerides
> 'A review of the controlled clinical trials and the post marketing
> safety data base resulted in no statistically significant adverse effects
> of Seroquel on cholesterol, LDL and triglycerides.
>
> 3. Although it is widely accepted that the the atypical
> antipsychotics have the same efficacy, Seroquel has the best tolerability.
> 'A review of the literature has shown widespread acknowledgment that
> the atypicals have similar efficacy. [I'm not sure how else we'd put this
> in the absence of direct head to head's with Seroquel] This paper has
> shown that Seroquel has an excellent tolerability profile, not only does
> it have placebo levels of EPS across the dose range, has no prolactin
> elevation and is weight neutral, but Seroquel has no metabolic issues* '
>
> *diabetes and lipids
>
> Wayne have you looked at diabetes and lipids?
> Martin would you like to add to the above?
>
>
> Kind regards Richard
> Richard Olbrich PhD
> Medical Affairs Manager- Seroquel
> PS&L
> AstraZeneca
> Alderley House Alderley Park
> Macclesfield Cheshire SK10 4TF
> United Kingdom
> Tel: +44 (0) 1625 515219
> Fax: +44 (0) 1625 515682
> Email richard.olbrich@astrazeneca.com
>
>
> -----Original Message-----
> From: Sayce, Rod
> Sent: Monday, 19 November, 2001 21:06
> To: Olbrich, Richard
> Cc: Owen, Richard T
> Subject: RE: Metabolic issues
>

> Dear Richard,
>
> Thanks for this. I believe that we have enough material for
> a review of the diabetes issue alone, without all the other parameters.
> However, without going overboard I think we could make a case for a review
> of the metabolic parameters for quetiapine - separately, CMC have
> suggested a safety update looking at all adverse events.
>
> Are you aware of any analyses that we have done looking at
> lipids? I know we have material that CMC are preparing at the moment on
> prolactin. Are we doing too much if we include this?
>
> I guess the next step will be to ask Goran's team to provide
> us with additional analysis - or is that up to Russell Giddins to provide?
> I presume Wayne Geller will also need to be involved at some point? I will
> then forward the information to CMC to start producing an outline of what
> we might want.
>
> I think Lou Aronne would be good if we focus on the weight
> issue, but I would like to see a diabetologist involved - my first point
> of contact would be John Buse of Chapel Hill, North Carolina, or Julio
> Rosenstock (Dallas, Texas) to identify someone who might be interested in
> helping us with the manuscript. If we are going to include a lot of lipid
> data, we might want to go to a cardiologist as well REDACTED
> REDACTED
>
> Would appreciate your thoughts ...
>
> Thanks,
>
> Rod
>
> -----Original Message-----
> From: Olbrich, Richard
> Sent: Friday, November 16, 2001 10:29 AM
> To: Sayce, Rod
> Subject: RE: Metabolic issues
> Importance: High
>
> Rod yes I did receive it please find enclosed:
>
> << Message: FW: regulatory defence document for
> diabetes >>
>
> Kind regards Richard
> Richard Olbrich PhD
> Medical Affairs Manager- Seroquel
> PS&L
> AstraZeneca
> Alderley House Alderley Park
> Macclesfield Cheshire SK10 4TF
> United Kingdom
> Tel: +44 (0) 1625 515219
> Fax: +44 (0) 1625 515682
> Email richard.olbrich@astrazeneca.com
>
>
> -----Original Message-----
> From: Sayce, Rod
> Sent: Friday, 16 November, 2001 15:26
> To: Olbrich, Richard
> Cc: Owen, Richard T

> Subject: Metabolic issues
>
> Dear Richard,
>
> I discussed this briefly during the COT, and on
> returning to work (at home today), I realize that I have not received a
> copy of the regulatory defence document - can you tell me if you ever
> received a copy? If not, I can chase up with Wayne on Monday.
>
> Many thanks,
>
> Rod
>
> -----Original Message-----
> From: Aked, Dominic M
> Sent: Saturday, September 15, 2001 4:57 AM
> To: Sayce, Rod; Hagger, Simon; Fitton, Lesley R
> Cc: Oldham, Alex; Brecher, Martin; 'Rebecca
> Bowen (E-mail)'; Holdsworth, Debbie; Owen, Richard T; Olbrich, Richard;
> Rice, Moira M
> Subject: RE: Dom re: metabolic issues
>
>
> Hi Rod, Simon and Lesley
>
> Can we discuss the proposed publication by Martin,
> and how we move this forward. I'll ask Alwyn to set up a teleconference
> for early next week.
>
> Richard (Olbrich): could you please liase with Wayne
> Geller or Russell Giddins, and obtain a copy of the regulatory defence
> document for diabetes
> Richard (Owen): could you please work with Moira to
> obtain the relevant literature searches.
>
> Lesley we will need to look at the data base, so we
> will need your guidance on who can do this work.
>
> Thanks for your help
>
> Kind regards
>
> Dom
>
>
>
>
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 18:40
> To: Aked, Dominic M; 'Rebecca Bowen (E-mail)'
> Cc: Oldham, Alex; Olbrich, Richard; Owen,
> Richard T
> Subject: RE: Dom re: metabolic issues
>
> Dom,
> We should include data regarding choleaserol, LDL
> and triglycerides. I suspect we haven't reviewed this in a while. Please
> confirm. If need confirmed I'll ask Wayne to look at Clintrace and we
> would need Emma and Karen to look at trial data base. We will also need
> to do a comprehensive publication review. Also suggest we designate a

> senior writer to put it together and to put it towards the top of the todo
> list. We will also probably want a OL on the paper. None of the
> psychiatry OL's really know this area which is medical not psychiatric.
> Wirshing has published, but he's not predictable. Suggest we get a
> friendly endocrinologist or internist-perhaps Lou Aronne who was on the US
> obesity ad board last December. We probably also need to get Adam
> Richards on board too.
> Martin
>
> -----Original Message-----
> From: Aked, Dominic M
> Sent: Friday, September 14, 2001 6:51 AM
> To: Brecher, Martin; Rebecca Bowen (E-mail)
> Cc: Oldham, Alex; Olbrich, Richard; Owen,
> Richard T
> Subject: Dom re: metabolic issues
> Importance: High
>
> Hi Martin
>
> Some thoughts.
>
> I strongly expect Janssen will drive this message in
> their marketing activities, as it delivers clear differential advantage
> over Zyprexa. We will need to counter this, as customers will want to
> make a comparison amongst the atypicals.
>
> The need to monitor blood glucose is also being
> debated, which could greatly influence doctors' prescribing.
>
> Therefore, I agree addition communications (e.g.
> publication as you suggest) would be helpful
>
> The data/messages we have been working with to-date
> are highlighted below. These data are as compelling as the Risperidal
> data, and therefore it is hoped that the marketing companies are
> responding to Janssen messages in the 'market place'. Perhaps we could
> raise the awareness of the MCs on this subject, and ask the top 10 (?) MCs
> what the situation is in their markets. These e-mails could form teh basis
> of a communication from one of teh GBMs (Simon?).
>
> We (the MAMs) will look at the regulatory defence
> document to see if there is anything more we can use promotionally.
>
> Kind regards
> Dom
>
> General information on diabetes
> * In the general population, the NHIS 1994 diabetes rate was 1.2% for
> persons aged 18-44 and 6.3% for persons aged 45-64
> * In patients with schizophrenia, 9-14% have current treated diabetes
>
> Seroquel - extremely low incidence of diabetes
> mellitus
> (post-marketing data)
> * Approximately 623 000 patients received Seroquel between launch in
> the US (1997) and May 2000
> * Only 12 cases of diabetes mellitus reported
>
> Seroquel - low incidence of adverse events possibly
> related to changes in glucose metabolism
>

>
> << File: weight change new.ppt >> << File:
> Weight gain.doc >>
> Seroquel is not associated with diabetes or its
> exacerbation
>
> << File: DoF AZ_S089.doc >>
> Number and percentage of Seroquel-treated patients
> in short-term controlled Phase II/III clinical trials with adverse events
> possibly related to changes in glucose metabolism.
> Seroquel N=1450 Placebo
> N=206 Haloperidol N=279 Clorpromazine N=100
> Diabetes melitus 0% 0%
> 0% 0%
>
> Number and percentage of Seroquel-treated patients
> in long-term controlled Phase II/III clinical trials with adverse events
> possibly related to changes in
> glucose metabolism.
> Seroquel n=260 Haloperidol
> n=41
> 0% 0%
>
>
> Janssen are making the following claims:
>
> Incidence of diabetes <1%
> Double blind trials Risperidal 0.0%
> Placebo 0.0%
> n=1838
> n=195
>
> Double blind + Risperidal 0.2% N/A
> open-label trials n=2607
>
> No need for serum glucose monitoring
>
>
> Diabetes: a concern with seleected newer
> antipsychotics
> * Occurs with or without weight gain
> * Occurs regardless of family history
> * Up to 50% of people with type 2 diabtetes are undiagnosed
> * Short and long-term health complications from diabetes: skin
> infections; retinopathy/cataracts; cadiovascular disease; increased
> mortality risk
> Evaluate diabetes risk of selected antipsychotics
>
> Adverse events reported since market introduction
> that were temporally (but not necessarily) related to Risperidal therapy
> include diabetes mellitus aggravated, including diabetisc ketoacidosis.
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 03:39
> To: Aked, Dominic M; Bowen, Rebecca
> Cc: Oldham, Alex
> Subject: metabolic issues
>
> << Message: Seroquel Pre-SERM Information >>
> Dom, Rebecca,
> 2 small streams of information have come my way.

> First is an advertisement from a psych journal from Janssen claiming no
> diabetes with risperidone. Second is a bibliography received yesterday
> (attached) with includes abstacts of several articles characterizing small
> patient samples in which clozapine and olanzapine had adverse effects on
> cholesterol, LDL, triglycerides, insulin levels, blood glucose and the
> incidence of diabetes. Quetiapine as best I can tell from the abstracts
> comes off as a lesser offender. Risperidone is not linked to these
> events. I therefore would like your views whether we should do a review
> of our data designed to lead to a publication where we add no adverse
> metabolic consequences to our preferred safety profile along with EPS,
> prolactin weight and QT.
> We have already submitted a regulatory defense
> showing no effect of Seroquel on random blood glucose and no signal of new
> diabetes or hyperglyemia.
> Trials 41 (SR pivotal) and 43 (risperidone
> comparator) measure fasting blood glucose and trial 43 also measures
> fasting cholesterol, LDL and triglycerides.
> To rephrase the question, Is there a perception of a
> clinical issue on metabolism with Seroquel and do we need to try to put a
> stake in the ground as soon as possible and in advance of the Trial 43
> data?
> Thanks
> Martin
>
> PS I wrote this prior to reading your mail regarding
> the Semyak, Wilson (included among the refs) and Casey posters which are
> consistent with the data cited above.
>
>
> -----Original Message-----
> From: Brecher, Martin
> Sent: 14 September 2001 03:39
> To: Aked, Dominic M; Bowen, Rebecca
> Cc: Oldham, Alex
> Subject: metabolic issues
>
> << Message: Seroquel Pre-SERM Information >>
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> incidence of diabetes. Quetiapine as best I can tell from the abstracts
> comes off as a lesser offender. Risperidone is not linked to these
> events. I therefore would like your views whether we should do a review
> of our data designed to lead to a publication where we add no adverse
> metabolic consequences to our preferred safety profile along with EPS,
> prolactin weight and QT.
> We have already submitted a regulatory defense
> showing no effect of Seroquel on random blood glucose and no signal of new
> diabetes or hyperglyemia.
> Trials 41 (SR pivotal) and 43 (risperidone
> comparator) measure fasting blood glucose and trial 43 also measures
> fasting cholesterol, LDL and triglycerides.
> To rephrase the question, Is there a perception of a
> clinical issue on metabolism with Seroquel and do we need to try to put a
> stake in the ground as soon as possible and in advance of the Trial 43
> data?
> Thanks
> Martin

Read it - Trial 41?

>
> PS I wrote this prior to reading your mail regarding
> the Semyak, Wilson (included among the refs) and Casey posters which are
> consistent with the data cited above.

EXHIBIT 28

Clinical Study

The weight profile of SEROQUEL over the long term

Authors: Brecher M, Rak IW, Melvin K, et al.

Title: The long-term effect of quetiapine (Seroquel®) monotherapy on weight in patients with schizophrenia.

Journal: *International Journal of Psychiatry in Clinical Practice*. 2000;4:287-291.

Seroquel®
quetiapine fumarate 25 mg, 100 mg, 200 mg & 300 mg tablets

Study design

- Retrospective analysis of SEROQUEL monotherapy in placebo-controlled and open-label extension trials
- 427 patients with schizophrenia received a mean daily dose of 475 mg of SEROQUEL after one year of open-label treatment
  - 178 of the 427 patients were treated with SEROQUEL for a minimum of 6 months (mean duration = 18.6 months)
  - Weight was recorded at baseline and end point
- Body weight was assessed by baseline body mass index (BMI) categories established by the National Heart, Lung, and Blood Institute of the National Institutes of Health
  - BMI defines weight relative to height
- All concomitant antipsychotic medication was stopped prior to entry into clinical trials

Favorable weight profile unaffected by higher doses of SEROQUEL in this study

- SEROQUEL did not result in clinically significant mean weight gain at any dose
- No correlation between higher doses and long-term mean weight changes

Minimal treatment withdrawal

- Only 1 patient in 427 (0.22%) withdrew due to weight gain

In short-term studies, only dyspepsia, weight gain, and abdominal pain were reported at a significantly higher incidence with increasing doses of SEROQUEL.

Favorable weight profile over time

- Clinically insignificant weight changes over the long term (mean duration = 18.6 months) demonstrated by BMI categories

Weight changes from baseline to end point* by baseline BMI category

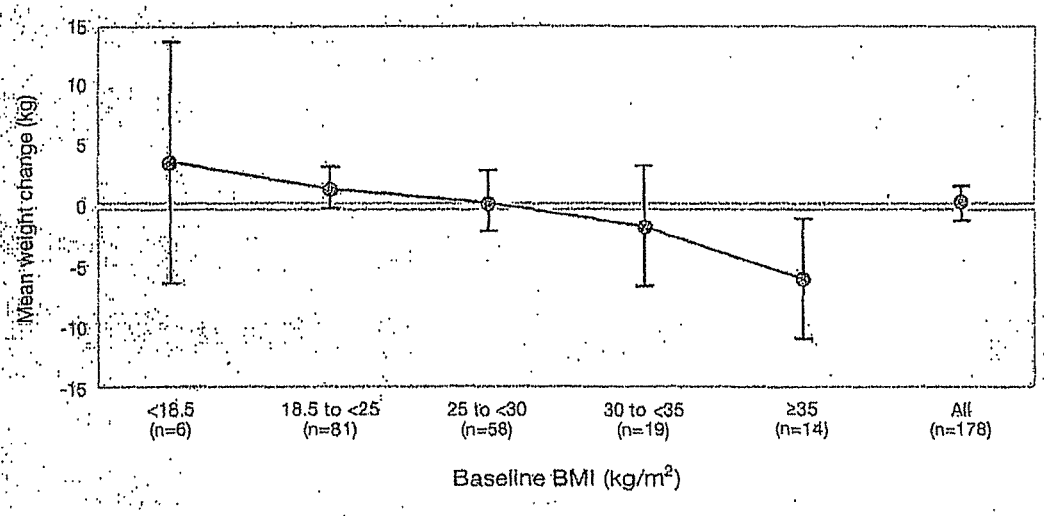
Baseline BMI (kg/m^2)	Number of patients	Mean daily dose at end point (mg)	Mean duration of treatment (days)	Mean weight change (kg)
<18.5	6	443	540	3.75
18.5 to <25	81	468	539	1.6
25 to <30	58	466	607	0.53
30 to <35	19	514	551	-1.53
≥35	14	483	543	-5.76
All	178	473	563	0.41

*Final recorded weight measurement.

Little overall effect on weight across BMI categories

- SEROQUEL demonstrates a favorable weight profile in every weight category (from underweight to obese)

Mean change in weight by baseline BMI category



The long-term effect of quetiapine (Seroquel™) monotherapy on weight in patients with schizophrenia

M BRECHER,[1] IW RAK,[1] K MELVIN[2] AND AM JONES[2]

AstraZeneca, [1]Wilmington, DE, USA and [2]Alderley Park, Macclesfield, Cheshire, UK

Correspondence Address
Dr Martin Brecher, AstraZeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE, USA
Tel: +1 (302) 886 2634
Email: martin.brecher@astrazeneca.com

Received 2 May 2000; revised 3 November 2000; accepted for publication 3 November 2000

INTRODUCTION: *Quetiapine (Seroquel™) is an atypical antipsychotic drug with demonstrated efficacy and tolerability. In particular, placebo-level extrapyramidal symptoms (EPS) across the entire dose range and a low propensity to cause sexual dysfunction suggest it may be associated with greater patient acceptability than alternative treatments. However, other side-effects, such as weight gain, may also have a significant impact on treatment acceptability.*

METHOD: *We report the long-term weight changes observed in a cohort of 427 patients with schizophrenia from controlled and open-label extension (OLE) trials, in which quetiapine (mean dose 475 mg/day after 1 year) was the only antipsychotic medication during the OLE period.*

RESULTS: *In these patients, there was no overall effect on weight across the body mass index (BMI) spectrum. There were no dose-related effects on weight, and only one patient withdrew from treatment due to an adverse event of weight gain. Quetiapine appeared to have a weight-neutral or 'normalizing' effect, with a tendency towards favourable shifts in bodyweight in underweight patients (BMI* < 18.5 kg/m^2) and severely obese patients (BMI ≥ 35 kg/m^2).

CONCLUSION: *These results indicate that long-term weight changes with quetiapine monotherapy are minimal and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents.* (*Int J Psych Clin Pract* 2000; 4: 287–291)

Keywords
atypical antipsychotics *quetiapine*
schizophrenia *weight gain*
Body Mass Index *long-term therapy*

INTRODUCTION

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. Conventional antipsychotic agents have been prescribed extensively over the last 40 years to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms) (EPS) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment.[1,2] Such adverse effects of the older, typical antipsychotics caused great distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% within 2 years.[3]

Many of the newer, atypical antipsychotic agents have an improved tolerability profile, and are less likely to cause debilitating EPS than are the earlier antipsychotic agents.[4] However, there are marked differences between compounds: quetiapine, for example, has a particularly favourable EPS profile,[4] with an incidence of EPS no different from placebo across the entire dose range.[5]

Seroquel is a trademark, the property of the AstraZeneca Group of Companies.

Quetiapine also has a low propensity to cause hyperprolactinaemia or sexual dysfunction.[4] These properties suggest that quetiapine may be more acceptable to patients than alternative treatments.[6] Other side-effects, including a tendency to induce weight gain, have been observed to varying degrees with most atypical antipsychotics.[7] Weight gain may also adversely affect patients' quality of life and compromise treatment compliance.

The association between antipsychotic medication and weight gain has been recognized for more than 40 years.[8] Historically, weight gain has been linked to efficacy of antipsychotic medication, with increased weight being linked to a positive outcome. However, more recent research suggests this may not be the case.[9,10]

Weight gain is associated with increased morbidity and mortality in a wide range of conditions, including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnoea and respiratory problems.[11,12] It is also linked with morbidity related to the disease being treated. Studies have shown that weight gain causes relatively more distress than many of the other side-effects commonly associated with antipsychotic medication.[13,14] If weight gain is considered unacceptable to the patient, then compliance may be compromised, potentially exacerbating the psychotic condition.

The extent to which antipsychotics are associated with weight gain varies considerably.[7,15] Weight gains of 4.45, 4.15, 2.10 and 2.16 kg have been observed following 10 weeks' treatment with clozapine, olanzapine, risperidone and quetiapine, respectively.[15,16] However, the true clinical significance of weight gain is observed in the context of long-term treatment. It is clear that long-term treatment with some antipsychotics (in particular clozapine and olanzapine) is associated with considerable increase in weight.[9,17] Given the growing importance of this issue, the present review assesses weight changes in patients with schizophrenia during long-term treatment with quetiapine monotherapy, focusing particularly on the potential effects exerted by dose or related to Body Mass Index (BMI).

METHODS

Weight data were analysed from controlled and uncontrolled clinical trials of quetiapine and the respective open-label extensions (OLE). Patients with psychotic symptoms were evaluated for eligibility to enter controlled and uncontrolled studies of quetiapine according to the inclusion and exclusion criteria of the particular study. Following the clinical trial, patients were allowed to enter into an open-label extension phase, where appropriate. Data from all patients who had a DSM-IV diagnosis of schizophrenia are included in the current review.

All concomitant antipsychotic medication was stopped prior to entry into the clinical studies, and treatment was with quetiapine monotherapy throughout both the double-blind and OLE periods of all studies.

Weight was assessed at baseline in most patients and at least once during follow-up, which varied across trials, ranging from 6 weeks to beyond 18 months. Consequently, the numbers of patients do not indicate the length of follow-up, and patients were not assessed following withdrawal of therapy. Baseline Body Mass Index (BMI) was available for most patients. For analysis, patients were grouped according to the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's standard categories for BMI.

STATISTICAL ANALYSIS

Weights were summarized using a last-observation-carried-forward approach within specified time intervals. Since the present exploratory analysis was designed only to highlight apparent contributors to weight change, rather than to provide a definitive analysis of predictors of weight change, no formal statistical analysis was performed on these data.

RESULTS

Weight data were analysed from 427 patients with schizophrenia from controlled and OLE studies in which only quetiapine was allowed as antipsychotic medication throughout the double-blind and open-label extension phase of each study. Patients received a mean daily quetiapine dose of 475 mg after one year of open-label treatment. Patient demographics are presented in Table 1.

Minimal overall weight change was observed over 18 months of treatment with quetiapine. The mean weight change from baseline was: 1.58 kg after 9–13 weeks (n=170); 0.26 kg after 14–26 weeks (n=165); 1.66 kg after 27–39 weeks (n=134); −1.53 kg after 40–52 weeks (n=41); and 1.94 kg after 53–78 weeks (n=146). (Note: patients did not necessarily have weight recorded at all timepoints.)

Table 1
Patient demographics

Number of patients (n)	427
Male/female (n)	277/150
Age, years (mean ± SD)	37.3 ± 10.8
Age distribution (N)	
<65 years	425
≥65 years	2
Weight, kg (mean ± SD)	75.21 ± 15.55
Weight distribution (n)	
Data not collected	28
≤50 kg	53
50–70 kg	171
71–90 kg	164
>90 kg	59

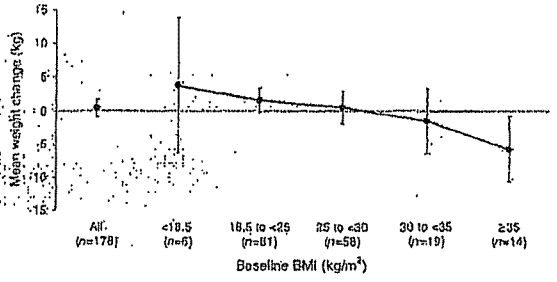


Figure 1
Mean change in weight, and associated 95% CI, from baseline to endpoint by baseline BMI category in patients treated with quetiapine monotherapy for at least 6 months (n=178). Mean treatment duration 18.6 months; mean daily dose 473 mg.

Effect of Baseline Body Mass Index

The mean change in weight from baseline to endpoint and associated 95% confidence intervals are shown in Figure 1 for each baseline BMI category for those patients who received at least 6 months' treatment with quetiapine (mean duration 18.6 months), and whose weight was recorded at baseline and endpoint. The mean dosage and duration of treatment are shown in Table 2 for each baseline BMI category. These data indicate that long term treatment with quetiapine has very little overall effect on weight, and the overlap of the 95% CIs with the zero change line allows quetiapine to be characterized as weight-neutral. Moreover, there is a tendency towards beneficial shifts in body weight in patients with BMI <18.5 kg/m^2 and in those with BMI ≥ 35 kg/m^2.

Longitudinal Analysis of Weight Change by Dose

Any effect of quetiapine dose on weight was investigated by analysing weight at baseline and endpoint for each of three dosage groups. The endpoint value was defined for each patient as the final recorded weight measurement that was taken. Patients were included in this analysis only if a baseline weight value had been obtained and if there was at least one other non-baseline value. Weight changes by dose group are presented in Figure 2, using the modal dose value for the last recorded weight value. These longitudinal data and associated 95% confidence intervals (CI) show there is no effect of quetiapine on weight at any dose, nor is there any correlation between increasing dose and mean long-term weight changes. These results are consistent with those from a short-term dose-ranging study reported previously.[5,16]

Effect of Gender

No clinically significantly different changes in weight from baseline to endpoint were observed between male and female patients on long term treatment with quetiapine. Weight changes of -0.58 kg and 1.94 kg were observed in male (n=108) and female (n=70) patients, respectively.

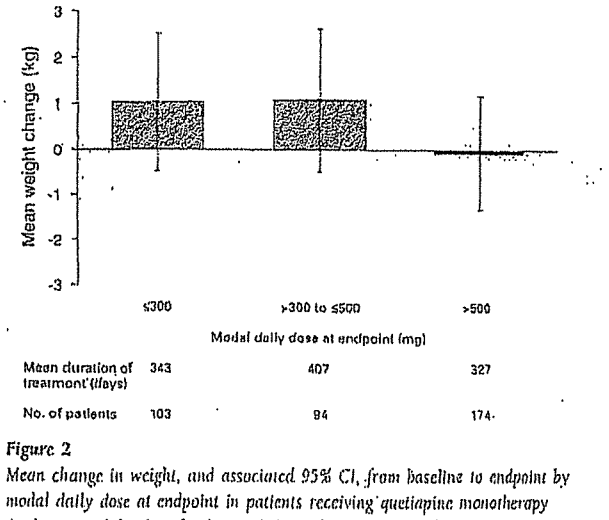


Figure 2
Mean change in weight, and associated 95% CI, from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy (endpoint is defined as final recorded weight measurement)

Withdrawals Due to Weight Gain

Only one patient withdrew (0.22%) as a result of an adverse event of weight gain.

DISCUSSION

Results of the present analysis show that, in clinical studies where no other antipsychotic medications were permitted during the OLE phase of treatment, quetiapine was associated with only minimal changes in weight in the short term (8 weeks), and with an overall neutral effect on weight with long-term treatment. By comparison, an increase of approximately 12 kg has been reported after 12 months' treatment with olanzapine 12.5–17.5 mg/day.[17]

BMI is widely accepted as being the most clinically appropriate measure of weight change, since it describes relative weight for height, and our analysis of the weight change profile by baseline BMI shows that in the long term (18 months), weight changes in all but the severely obese (BMI >35 kg/m^2; Obesity Category II) are small, with 95% CIs overlapping the zero change line. Indeed, in this severely obese group, long-term quetiapine therapy was associated with a favourable weight loss. In addition, there was a trend towards beneficial weight gain in underweight patients (BMI <18.5 kg/m^2). Quetiapine appears therefore to be associated with potentially beneficial shifts in body weight towards normal values when individual BMI categories are considered.

Table 2
Weight changes from baseline to endpoint[a] by baseline BMI category in patients treated for at least 6 months with quetiapine monotherapy

Baseline BMI (kg/m²)	n	Mean daily dose at endpoint (mg)	Mean duration of treatment (days)	Mean change in weight (kg)
All	178	473	563	0.41
<18.5	6	443	540	3.75
≥18.5 <25	81	468	539	1.6
≥25 <30	58	466	607	0.53
≥30 <35	19	514	551	−1.53
≥35	14	493	543	−5.76

[a]Final recorded weight measurement

Weight gain with certain antipsychotics (such as clozapine and olanzapine) has been associated with the development of diabetes.[18] In this context it is interesting to note that the addition of quetiapine to ongoing clozapine therapy in 65 patients significantly improved glycaemic status in the 20% of patients who had developed diabetes while on clozapine monotherapy.[19] Furthermore, these 65 patients had also experienced a 6.5 kg mean increase in weight during 6 months of clozapine monotherapy. Addition of quetiapine to the treatment regimen resulted in a mean weight loss of 4.2 kg over the subsequent 10 months.

Although various theories have been proposed, the precise mechanism(s) involved in the induction of weight gain by atypical antipsychotic agents has not been fully elucidated. It may be a multifactorial process, with involvement of serotonergic, histaminergic and/or adrenergic neurotransmission. Olanzapine and clozapine, which appear to be associated with comparatively large increases in weight,[9,15,18,20] have been shown to increase circulating leptin levels,[21,22] which correlate positively with increased BMI.

Antipsychotics also vary in the time course of their effect on weight gain. Weight changes occurring in the first weeks of treatment, particularly in patients who have previously been untreated, have important implications for compliance with long-term antipsychotic medications.[23] In this regard, therefore, quetiapine would appear to have a significant advantage over other antipsychotics. In a retrospective analysis, risperidone-treated patients reached a weight plateau after approximately 12 weeks, whereas clozapine- and olanzapine-treated patients showed continued increase in weight over a longer period (20 weeks).[7] In contrast, the present analysis demonstrates that quetiapine is associated with only a minimal change in weight that does not appear to be dose-related, does not increase over time, and does not appear to affect compliance. Indeed, in a recent study of patients' satisfaction with quetiapine, the combination of efficacy and a favourable tolerability profile was reflected in high levels of satisfaction and acceptance of long-term treatment, and a normalization of eating habits in 73% of the study population.[6] Given the association of weight gain with increased morbidity and mortality from hypertension and macrovascular disease,[11,12] and its detrimental impact on patients' well-being,[13,14] quetiapine's overall neutral or 'normalizing' effect on weight in the long term may have wider implications for patients' overall health, and associated healthcare costs.

In conclusion, weight changes in patients treated long term with quetiapine when used as monotherapy are neutral and potentially beneficial, and do not appear to raise the medical concerns associated with some other atypical agents. Combined with quetiapine's balanced combination of efficacy and tolerability, the present analysis suggests that quetiapine has a favourable benefit – risk profile as a first-choice antipsychotic in the long-term treatment of schizophrenia.

KEY POINTS

- While the impact of weight gain during long-term antipsychotic therapy is an important consideration when treating patients with schizophrenia, the extent to which individual agents are associated with weight gain varies considerably.
- Long-term quetiapine monotherapy showed no overall effect on weight across the BMI spectrum, with 95% CIs encompassing zero weight change in all BMI categories apart from the severely obese (BMI ≥35 kg/m²), in whom weight loss was observed. Any weight changes with quetiapine therapy showed no association with dose or gender.
- Long-term monotherapy with quetiapine is associated with a potentially 'normalizing' effect on weight, with a tendency towards weight gain in underweight patients and weight loss in severely obese patients.
- The combination of efficacy, good tolerability and an overall neutral long-term effect on weight suggests that quetiapine should be considered a first-choice antipsychotic in the long-term treatment of schizophrenia.

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EXHIBIT 29

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

November 2002
NO. 02-5

Dear Dr. Letter

Diabetic ketoacidosis and diabetic coma due to an increase in blood glucose level during administration of Seroquel® 25mg, 100mg tablets (quetiapine), an antipsychotic drug

Since February 2001 when Seroquel was started to be marketed, 12 serious cases (including 1 death) of hyperglycaemia, diabetic ketoacidosis, and diabetic coma where causality with the drug could not be ruled out have been reported (estimated number of patients who used Seroquel of the end of September 2002 was approximately 130,000). Hyperglycaemia was added in the "Precautions for use" to call attention in July 2002; however, based on the discussion of serious cases, "Contraindication" and "Precautions for use" were revised, and "Warning" was added to the package leaflet. This drug should be cautiously administered with strict attention to the following instructions. If Adverse reaction as above is confirmed, please contact the person in charge of Drug Information of Fujisawa which is the marketing company for Japan.

Manufacturing company: AstraZeneca K.K.
Marketing company: Fujisawa Pharmaceutical Co. Ltd.

1. **Seroquel must not be administered to patients with diabetes or a history of diabetes.**

In diabetic patients or patients having a history of diabetes, blood glucose levels may elevate, which may rapidly aggravate metabolic conditions. This drug must not be given to such patients.

2. **During administration of Seroquel, the patient should be monitored carefully including measurement of blood glucose levels.**

During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration of the drug may cause serious adverse reactions such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.

3. **Information on the adverse reactions and action to be taken must be fully explained to the patient and the family.**

Prior to administration of the drug, sufficient explanation should be provided to the patient and the family that significant adverse reactions including diabetic ketoacidosis and diabetic coma may occur. They should be instructed to stop administration of the drug and visit hospital if any symptoms such as thirst, polydipsia, polyuria, increased urinary frequency or others appear.

"Warning", "Contraindication" and "Precautions for use" were revised on the underside of the leaflet.

Contact : Post-Marketing Surveillance 1, Fujisawa Pharmaceutical Co., LTD.
1-6, Kashima 2-Chome, Yodogawa-ku, Osaka, Japan, 532-8514
Phone: +81-6-6390-5266
Fax: +81-6-6304-1319

(Narratives)
Not fixed

No.	Sex, age, reason for use [Complication]	Clinical course and treatment
1		
	Concomitant drugs:	
2		
	Concomitant drugs:	
3		
	Concomitant drugs:	
4		
	Concomitant drugs:	

DEAR DOCTOR LETTER

- EMERGENCY SAFETY INFORMATION -

Dear Dr. Letter

"Warning", "Contraindication" and "Precautions for use"

"Warning", "Contraindication" and "Precautions for use" were revised as follows. This revision is based on the post-marketing incidence of hyperglycaemia.

[Warning]

1. During administration of this drug, the patient must be carefully observed, and blood glucose levels should be measured, because marked elevation of blood glucose after administration may cause significant side effects such as diabetic ketoacidosis and diabetic coma, and in some cases, death may occur.
2. Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency and also instructed to stop administration of the drug and visit hospital if any of these symptoms appear. [See "Important basic precautions"]

[Contraindication] The drug must not be given to the following patients.

5. Patients with diabetes or a history of diabetes

[Precautions for use]

1. Careful administration (The drug should be given with particular caution in the following patients.)

(6) Patients with a family history of diabetes, or those having diabetes risk factors such as hyperglycaemia or obesity [See "Important basic precautions"]

2. Important basic precautions

(1) Administration of the drug may markedly increase blood glucose, in some patients, leading to life-threatening clinical courses including diabetic ketoacidosis or

diabetic coma. During administration of the drug, blood glucose levels should be measured, and thirst, polydipsia, polyuria, increased urinary frequency and others should be fully monitored. Especially for the patients with diabetes risk factors such as hyperglycaemia or obesity, increased blood glucose may rapidly aggravate metabolic conditions.

(2) Prior to administration of the drug, sufficient explanation should be provided to the patient and the family to notify that the above serious side effects may occur. They should be advised to note abnormalities such as thirst, polydipsia, polyuria, and increased urinary frequency, and also instructed to stop administration of the drug if such a symptom may appear, and visit hospital.

(3) Administration of the drug may increase body weight. Pay attention to obesity, and if a sign of obesity is observed, appropriate action including diet therapy or exercise therapy should be taken.

3. Adverse Reactions

(1) Clinically significant adverse reactions

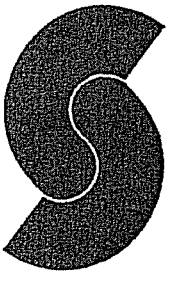
1) Hyperglycaemia, diabetic ketoacidosis, and diabetic coma: Hyperglycaemia may appear, and occurrence of diabetic ketoacidosis or diabetic coma may lead to life-threatening clinical courses. Measurement of blood glucose and observation of thirst, polydipsia, polyuria, and increased urinary frequency should be fully carried out. If any abnormalities are found, administration should be stopped, and appropriate action such as administration of insulin preparations should be taken.

(Only revised parts are described.)

EXHIBIT 3

AstraZeneca Pharmaceuticals

Seroquel™
(Quetiapine)



Commercial Support Team - Technical Document (TD005)

CGI - Severity of Illness Meta-Analysis

Request From: Debbie Holdsworth

Date Requested: Jan 2000

Statistician/Statistical Programmer Responsible: Rob Hemmings

1 Source of Data

This document summarises initial findings into a meta-analysis of CGI - Severity of Illnes (SoI) scores taken from trials 5077IL/0013, 14, 50 and 52. As with all meta-analyses, care is required in choosing which combinations of trials can sensibly be interpreted. The data below comprises all our comparative data with Haloperidol (with the exception of trial 5077IL/0015 which assessed a significantly different patient population) and as such combines slightly different patient populations, inclusion / exclusion criterion, timings of endpoints, and doses of drug. This seems acceptable however, in order look for a general claim of superior efficacy for Seroquel over Haloperidol with regards CGI - SoI.

Any analysis of this data would be post-hoc.

2 Design of Trials/ Analysis Methods

2.1 Study Design

Table 1 gives a summary of the trials used and the pertinent design features from each trial.

Table 1

TRIAL	Treatments / Dose (# pats.)	Patient population	Inc/Exc criteria	Timing of endpoint
52 (PRIZE)	SER 600mg/day BD HAL 20mg/day BD (330 in total, 1:1 rand)	Schiz. pats. with history of partial response to trad anti-psychotic therapies	CGI, SoI >= 3	8 weeks after baseline
50 (ESTO)	SER up to 600mg/day BD HAL up to 20mg/day BD (190 in each tmt group)	Patients presenting with acute exacerbation of schiz. or schiz. disorder in last 3 years	CGI, SoI >= 4	12 weeks after baseline (also 24 and 52 weeks after baseline)
14	SER up to 800 mg/day BD HAL up to 16 mg/day BD (220 per group)	Acute exacerbation of subchronic or chronic schiz.	CGI, SoI >= 4	6 weeks after baseline
13	SER 75, 150, 300, 600, 750 mg/day TD HAL 12 mg/day TD PLACEBO (50 pats. per arm)	Hosp. patients with acute exacerbation of chronic or sub-chronic schiz.	CGI, SoI >= 4	6 weeks after baseline

Points to note are:

- Differing doses of SER and HAL across the trials;
- Slightly different patient populations (especially 52);
- Differing times of endpoint assessment.
- Data from the 75mg/day group has been excluded from trial 0013 as it is not in the therapeutic dose range for Seroquel.

2.2 Analysis Methods

Only descriptive summaries have been performed on this combined data. The only assumption made is that results can be sensibly interpreted when data from these trials are combined.

2.3 Details of SAS programs

Analysis programs from trials 13 and 14 are stored in the CDE under the CST directory (s:\d5077\filesm\CST) in two programs named TD5_G1 and TD5_G2. Analysis programs from trials 50 and 52 are in the CDE under the trial directory and are named as above.

3 Results

Before the data from these trials was considered for analysis, they were explored using standard summary statistics. The endpoints requested to be explored were: Change from baseline in Severity of Illness; and Proportion of patients with Severity of Illness ≤ 3 at endpoint.

Table T1 (Appendix A) shows the results of these summaries. Using either endpoint definition, it is clear that a claim of superiority for Seroquel over Haloperidol could not be generated using these data as the Haloperidol arm has a greater proportion of patients with lower CGI-SoI at endpoint and with greater reductions from baseline. It is noted, however, that a claim of 'equivalence' may be possible, given a prospective definition of clinical equivalence limits.

It was feared that messages from these trials may have been diluted by combining low and high doses of Seroquel. Therefore data from trials 13, 14, 15 and 50 were further explored, by taking only the following data:

Table 2 - Definition of 'High' doses of Seroquel for each of the trials

TRIAL	mg/day	
13	>= 600	i.e. ignoring the 75, 150 and 300 mg/day categories
14	>= 450	
50	>=450	
52	600	i.e. all available data

Results from these additional explorations are summarised in table T2 Appendix A (in addition, dose response results from trial 13 is summarised in Appendix B below). They do not suggest any different conclusions to those described above, i.e. that a claim of superiority is highly unlikely using these definitions, whilst a claim of equivalence is not ruled out.

A final hypothesis examined was that the effect of Seroquel relative to Haloperidol may be larger in patients with severe disease at baseline. Tables T3 and T4 in Appendix A are repeats of table T1 but for patients with baseline severity of 3-5 and 6,7 respectively.

4 Conclusions

The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of equivalence is not ruled out.

5 References

None

Appendix A: Statistical Appendix

Index of Tables Created

TABLE T1 Change from baseline and level of severity at endpoint in CGI-SoI scores

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	1	0	2	0	0	0	0	0	3	0	0.4	0
-4	0	1	4	12	4	5	2	1	10	19	1.5	3.5
-3	9	2	20	25	17	18	5	5	51	50	7.5	9.3
-2	22	8	44	53	26	33	21	14	113	108	16.6	20.0
-1	63	13	68	58	60	54	35	35	226	160	33.3	29.6
0	82	22	49	55	30	39	34	54	195	170	28.7	31.5
1	22	4	30	9	9	5	11	7	72	25	10.6	4.6
2	5	0	2	7	0	0	1	1	8	8	1.1	1.5
3	0	0	1	0	0	0	0	0	1	0	0.1	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									679	540	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	2	0	5	8	6	4	3	3	16	15	2.4	2.8
2	14	5	29	33	10	20	15	8	68	66	10.0	12.2
3	39	7	53	52	38	42	35	31	165	132	24.3	24.4
4	58	16	46	58	55	44	36	46	185	164	27.2	30.4
5	44	14	42	36	26	36	10	21	122	107	18.0	19.8
6	47	5	35	28	9	7	9	7	100	47	14.7	8.7
7	10	3	10	4	2	1	1	1	23	9	3.4	1.7
									679	540	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

TABLE T2 Change from baseline and level of severity at endpoint in CGI-SoI scores (high doses of Seroquel only)

Change from baseline in severity	TRIAL 13		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	0	0	0	0	0	0	0	0	0	0	0	0
-4	0	1	0	12	2	5	2	1	4	19	1.3	3.5
-3	2	2	2	25	4	18	5	5	13	50	4.1	9.3
-2	13	8	14	53	5	33	21	14	53	108	16.9	20.0
-1	34	13	20	58	12	54	35	35	101	160	32.2	29.6
0	40	22	17	55	11	39	34	54	102	170	32.5	31.5
1	14	4	10	9	3	5	11	7	38	25	12.1	4.6
2	2	0	0	7	0	0	1	1	3	8	0.1	1.5
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									314	540	100	100

Level of severity at endpoint	TRIAL 13		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
				n			n	n	n	n	n	n
1	0	0	0	8	2	4	3	3	5	15	1.6	2.8
2	8	5	2	33	2	20	15	8	27	66	8.6	12.2
3	20	7	19	52	8	42	35	31	82	132	26.1	24.4
4	24	16	13	58	14	44	36	46	87	164	27.7	30.4
5	25	14	13	36	7	36	10	21	55	107	17.5	19.8
6	22	5	14	28	3	7	9	7	48	47	15.3	8.7
7	6	3	2	4	1	1	1	1	10	9	3.2	1.7
									314	540	100	100

TABLE T3 Change from baseline and level of severity at endpoint in CGI-SoI scores (patients with baseline score of 3, 4 or 5)

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	0	0	0	0	0	0	0	0	0	0	0	0
-4	0	0	2	5	3	4	2	1	7	10	1.3	2.4
-3	7	1	16	14	7	9	4	5	34	29	6.5	6.9
-2	19	6	38	39	15	26	18	13	90	84	17.3	20.0
-1	48	9	56	46	49	44	32	31	185	130	35.6	30.9
0	51	17	30	37	24	33	30	50	135	137	26.0	32.5
1	18	2	24	9	7	5	11	7	60	23	11.5	5.5
2	5	0	2	7	0	0	1	1	8	8	1.5	1.9
3	0	0	1	0	0	0	0	0	1	0	0.2	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									520	421	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	1	0	3	8	6	4	3	3	13	15	2.5	3.6
2	14	4	27	26	9	19	15	8	65	57	12.5	13.5
3	37	6	49	41	28	33	34	31	148	113	28.5	26.8
4	45	14	41	44	44	37	33	46	163	141	31.3	33.5
5	32	10	29	25	15	26	7	16	83	77	16.0	18.3
6	18	1	19	10	3	2	6	4	46	15	8.8	3.6
7	1	0	1	3	0	0	0	0	2	3	0.4	0.7
									520	421	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

TABLE T4 Change from baseline and level of severity at endpoint in CGI-SoI scores (patients with baseline score of 6,7)

Change from baseline in severity	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
-5	1	0	2	0	0	0	0	0	3	0	1.9	0
-4	0	1	2	7	1	1	0	0	3	9	1.9	7.6
-3	2	1	4	11	10	9	1	0	17	21	10.7	17.6
-2	3	2	6	14	11	7	3	1	23	24	14.5	20.2
-1	15	4	12	12	11	10	3	4	41	30	25.8	25.2
0	31	5	19	18	6	6	4	4	60	33	37.7	27.7
1	4	2	6	0	2	0	0	0	12	2	7.5	1.7
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
									159	119	100.00	100.00

Level of severity at endpoint	TRIAL 13*		TRIAL 14		TRIAL 50		TRIAL 52		TOTAL n		TOTAL %	
	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL	SER	HAL
	n	n	n	n	n	n	n	n	n	n	n	n
1	1	0	2	0	0	0	0	0	3	0	1.9	0
2	0	1	2	7	1	1	0	0	3	9	1.9	7.6
3	2	1	4	11	10	9	1	0	17	21	10.7	17.6
4	3	2	5	14	11	7	3	0	22	23	13.8	19.3
5	12	4	13	11	11	10	3	5	39	30	24.5	25.2
6	29	4	16	18	6	5	3	3	54	30	34.0	25.2
7	9	3	9	1	2	1	1	1	21	6	13.2	5.0
									159	119	100.00	100.00

* Doses of SER have been combined - 75mg group has been excluded

Appendix B: Supporting Presentations

TABLE T5 - CGI-Sol Trial 0013

Level of severity at endpoint	DOSE (mg/day) SER 150	SER 300	SER 600	SER 750	HAL 12	PLA
	n	n	n	n	n	n
1	0	2	0	0	0	0
2	1	5	7	1	5	1
3	14	5	8	12	7	3
4	9	15	10	14	16	11
5	9	10	13	12	14	16
6	13	12	8	14	5	12
7	2	2	5	1	3	8

Change from baseline in severity	DOSE (mg/day) SER 150	SER 300	SER 600	SER 750	HAL 12	PLA
	n	n	n	n	n	n
-5	0	1	0	0	0	0
-4	0	0	0	0	1	0
-3	3	4	2	0	2	0
-2	4	5	7	6	8	2
-1	13	16	14	20	13	7
0	23	19	19	21	22	24
1	3	5	7	7	4	13
2	2	1	2	0	0	5
3	0	0	0	0	0	0
4	0	0	0	0	0	0

Technical Document (TD005)

Approved for issue by:

Andrew Gorman
Project Team Physician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

Emma Westhead
Senior Statistician
AstraZeneca Pharmaceuticals
Alderley Park
Macclesfield, Cheshire
SK10 4TG

Signature.....Date.....

EXHIBIT 30

Objection Handler on
Atypical antipsychotics and glucose dysregulation

By Dr Richard Owen
Global Medical Affairs Manager-Seroquel

With contributions from: Rebecca Bowen (Global Brand Director)
Dr Chip Altman (Global Commercial Physician)
Alison Wilkie (Global Communications Manager

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Date issued : 26 November 2002 (version 1)

Summary

- **The literature contains much conflicting information concerning the prevalence of diabetes and glucose dysregulation with atypical antipsychotics. Most of the published evidence relates to clozapine and olanzapine.**

- **Product labels vary widely between countries concerning statements about diabetic risk-not only between products but for the same product in different countries.**

- **The company's safety database has reassuring data concerning Seroquel's diabetic potential and glucose regulation**

Background

Abnormalities in glucose regulation including diabetes mellitus can occur more commonly in schizophrenia patients compared with healthy individuals; a phenomenon which has been recognised even prior to the neuroleptic era. Hyperglycaemia, exacerbation of existing diabetes, new onset type 2 diabetes and diabetic ketoacidosis have been reported with a variety of atypical agents but the vast majority of reports are with clozapine and olanzapine.

This objection handler summarises the key publications in the literature to date, label statements and changes with our main competitors and summarises our data with Seroquel regarding diabetes and glucose dysregulation.

Summary of selected published data

A recent review by Henderson (CNS Drugs 2002; 16 (2): 77-89) reviews the evidence for atypical antipsychotic-induced diabetes mellitus.

Henderson.pdf

In summary their main conclusions was that most of the evidence of diabetogenic risk relates to clozapine and olanzapine. However the topic is complex and the literature is full of both supportive or dismissive evidence concerning the risk of hyperglycaemia and diabetes with atypicals. Only controlled trials will lead to a fuller understanding and such trials are at present uncommon.

It is interesting to note the different approaches by the various companies in relation to their antipsychotic. The approaches can be broadly summarised as follows:

Lilly- have tried to imply that diabetes/glucose dysregulation is a <u>class effect</u> of atypicals (in other words if olanzapine is going to be singled out as a culprit they intend to brand all the atypicals as guilty as well)!

Janssen and *Pfizer*- tried to imply that risperidone and ziprasidone are different to other atypicals in that it cause little or no problems with diabetes or glucose regulation. (Data cited in Henderson 2002). Moreover risperidone has been used without complications in patients with schizophrenia and comorbid diabetes.

BMS- have published retrospective audits showing that olanzapine and risperidone are associated with increased diabetic risk compared to typicals (but surprisingly did not mention their own drug aripiprazole in this audit).
See e.g. BMJ article by Koro et al 2002-11-22
Koro et al 2002
They have shown relatively little data on aripiprazole and glucose levels although data on fasting blood glucose levels from a 26 week study did not reveal any problems (see CME slide no.58 in Key Claims section in the aripirazole pyramid).
http://cns.ta.astrazeneca.net/pyramids/Aripiprazole/aripiprazole_Claims.htm

AZ- We have presented data on an audit by Gianfrancesco et al showing that the risk with olanzapine is greater than the risk with Seroquel, risperidone and conventional antipsychotics.
Gianfrancesco et al 2002
There are data from Reinstein et al (Clin Drug Invest. 1999; 18: 99-104) showing that the addition of Seroquel to a clozapine regime improved glucose metabolism in 20% of the 13 patients who developed diabetes on clozapine alone. We currently await the results of study 43 which will compare fasting blood glucose levels between Seroquel and risperidone.

A selection of recent literature on diabetes and antipsychotics is attached.


Rev-lit-diab.doc

Label statements/changes that have occurred for Seroquel and the competition

(a) Japan

Recently the Japanese regulatory authorities imposed label changes relating to diabetes and glucose dysregulation for both Zyprexa (in April 2002) and Seroquel(in November 2002). These essentially comprise a contraindication for these agents in patients with diabetes or a history of diabetes and a requirement for blood glucose monitoring. The attached icon contains details of the letter that was sent to clinicians in Japan explaining the change to the labelling.


Sero-japdeardr.doc

Risperidone recently had the word 'hyperglycaemia' added to the other ADR's section of its label in Japan. Clozapine aripiprazole and ziprasidone are not yet marketed in Japan.

(b) US

The table below gives the current US PDR classification of glucose related adverse events for marketed /soon to be marketed atypicals.

	Adverse event frequency	
Product	**Infrequent (0.1-1%)**	**Rare (<0.1%)**
Seroquel	Hyperglycaemia Diabetes mellitus	
Olanzapine	Diabetes mellitus Hyperglycaemia	
Aripiprazole	Diabetes mellitus Hyperglycaemia	
Risperidone	Diabetes mellitus	
Ziprasidone	Hyperglycaemia	Glucose tolerance decreased
Clozapine	Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatment in patients with no prior history of hyperglycemia. While a causal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL® (clozapine) who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of CLOZARIL® (clozapine) should be considered. Hyperglycaemia (<1%)	

(c) Europe

Seroquel

EU – the Pharmacovigilance Working Party of the CPMP reviewed the class in June 2001. Seroquel SmPC has language "Special Warnings and Precautions for Use" section stating that hyperglycaemia and exacerbation of preexisting diabetes has been reported in very rare cases and that appropriate clinical monitoring is advisable. Similar wording is also in the Undesirable Effects section.

In UK, discussions regarding these issues are pending with MCA and should be resolved by the end of the year

The Italian label includes warnings and precautions that hyperglycaemia and the exacerbation of pre-existing diabetes have been reported rarely, and that monitoring is advisable.

Olanzapine

The EU label for olanzapine states that elevated glucose levels are common (frequency 1-10%). In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels <7.8 nmol/l the incidence of non-fasting plasma glucose levels >11nmol/l (suggestive of diabetes) was 1.0% compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels >8.9nmol/l but <11mmol/l (suggestive of hyperglycaemia) was 2.0% compared to 1.6% with placebo. Hyperglycaemia is also reported as a very rare (<0.01%) spontaneous event.

Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Risperidone

The EU Pharmacovigilance Party of the CPMP has proposed similar wording to that for Seroquel mentioned above.

The current UK label makes no mention of diabetes or hyperglycaemia for risperidone.

Ziprasidone

From the Swedish label:

In a double-blind comparative study, metabolic parameters were measured including weight, fasting insulin, total cholesterol, triglycerides and an insulin resistance (IR) index. Among patients receiving ziprasidone no significant changes from baseline values were observed for any of these metabolic parameters".

Clozapine
From the UK SmPC:
Abnormalities of glucose homeostasis occur uncommonly in approximately 0.35% of CLOZARIL (clozapine) patients in the UK cohort monitored by the CLOZARIL Patient Monitoring Service. Severe hyperglycaemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL (clozapine) treatment in patients with no prior history of hyperglycaemia. Blood glucose levels normalised in most patients after discontinuation of CLOZARIL (clozapine), and a rechallenge in a few cases produced a recurrence of hyperglycaemia. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL (clozapine) particularly if symptoms of polydipsia, polyuria, and weakness develop. With prolonged treatment considerable weight gain has been observed in some patients and further investigation is periodically needed to ensure hyperglycaemia is not missed. In patients with significant treatment-emergent hyperglycaemia, the discontinuation of CLOZARIL (clozapine) should be considered when active medical management of the hyperglycaemia has failed.

Seroquel safety database analysis

Note: This summary has been adapted from a review of the company database and since adverse event data constantly changes only qualitative conclusions have been presented here.

- Adverse event data from over 3000 patients exposed to Seroquel during clinical trials has shown that the incidence of adverse events possibly associated with disturbances in glucose regulation is low, and does not increase as duration of exposure to Seroquel increases. No cases of diabetic ketoacidosis or hyperosmolar coma were reported, and a very small number of cases of diabetes mellitus were reported (all of which were considered by the investigator to be unrelated to trial treatment).

- Random plasma glucose data from clinical trials has shown that hyperglycemia (random glucose value $\geq$ 200 mg/dl) was observed in a small number of patients treated with Seroquel, but was not sustained, extreme, or associated with any symptoms. Further, the incidence of hyperglycemia did not increase as the duration of exposure to Seroquel increased. In addition, there were no statistically significant differences between Seroquel and placebo in the mean changes from baseline to endpoint in random plasma glucose levels.

- All the reports received from Japan are either confounded, or have alternative explanations or a negative dechallenge, or had documentation of hyperglycaemia or poor diabetes control prior to receiving Seroquel. These reports provide insufficient information to establish a causal relationship between Seroquel and diabetes, hyperglycaemia, exacerbation of diabetes, or diabetic ketoacidosis.

- Worldwide (including Japan) postmarketing reports comprise cases of new-onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, diabetic ketoacidosis or hyperglycaemia. However, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. This position is supported by the literature where the incidence of diabetes mellitus in the schizophrenic population is noted to exceed that in the general population, even prior to the introduction of atypical antipsychotic medications (Dixon L et al 2000; Schiz Bull.26 (4):903-912).

Company position

Seroquel has proven safety and efficacy – with over 4 million patient exposures to Seroquel worldwide.

There is no evidence to conclude that Seroquel causes glucose dysregulation, diabetes or worsens diabetes.

There is no evidence that glucose dysregulation is a class effect of atypical antipsychotics.

EXHIBIT 31

PERGAMON

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Psychoneuroendocrinology 28 (2003) 83–96

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A review of the effect of atypical antipsychotics on weight

H. Nasrallah *

Department of Psychiatry, University of Cincinnati Medical Center, 231 Albert Sabin Way, P.O. Box 670559, Cincinnati, OH 45267-0559, USA

Abstract

Controlled research trials have shown that atypical antipsychotics have important advantages over standard antipsychotics, including a broader spectrum of efficacy and improved tolerability profile, particularly with regard to neurological adverse events such as extrapyramidal symptoms (EPS). Some atypical antipsychotics, however, tend to cause significant weight gain, which may lead to poor compliance and other adverse health effects. The mechanisms involved in antipsychotic drug-related weight gain are as yet uncertain, although serotoninergic, histaminic, and adrenergic affinities have been implicated along with other metabolic mechanisms. The atypical antipsychotics vary in their propensity to cause weight change with long-term treatment. Follow-up studies show that the largest weight gains are associated with clozapine and olanzapine, and the smallest with quetiapine and ziprasidone. Risperidone is associated with modest weight changes that are not dose related. Given the equivalent efficacy of atypical antipsychotics, weight-gain profile is a legitimate factor to consider when constructing an algorithm for treatment due to the serious medical consequences of obesity.

Keywords: Atypical antipsychotics; Schizophrenia; Weight gain; Long-term therapy

* Tel.: +1-513-558-4615; fax: +1-513-558-4616.
E-mail address: HNasra2905@aol.com (H. Nasrallah).

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Contents

1. Introduction

Atypical antipsychotics are an important advance in the treatment of schizophrenia and other psychoses, and have become widely used as first-line pharmacotherapy for psychosis. One of the main advantages of the atypical antipsychotics over standard antipsychotics is their broad spectrum of efficacy. Unlike the older conventional antipsychotics, atypical antipsychotics are effective in the treatment of all schizophrenia domains (positive, negative, affective, and cognitive symptoms) (Javitt, 1999; Purdon et al., 2001). Conventional antipsychotics (e.g. haloperidol, chlorpromazine) do not always fully resolve positive symptoms, have little effect on negative symptoms, and may worsen cognitive symptoms in some patients (Spohn and Strauss, 1989; Purdon et al., 2001).

As with all drugs, efficacy must be accompanied by a tolerable side-effect profile to optimize clinical effectiveness. Extrapyramidal symptoms (EPS) are a major problem with conventional antipsychotics and often lead to poor compliance (Tran et al., 1997; Davies et al., 1998). Atypical antipsychotics, however, have been shown to cause less EPS than standard antipsychotics, although dose-related EPS do occur with some agents (Owens, 1994; Peuskens, 1995; Daniel et al., 1999). With the declining use of conventional antipsychotics and reduced incidence of acute EPS as well as tardive dyskinesia, other side effects of antipsychotics, such as weight gain, have become more prominent as impediments to clinical effectiveness.

Weight gain is associated with many conventional and some atypical antipsychotics (Allison et al., 1999a) and its degree is dependent on the drug and the individual patient. Weight gain occurs shortly after starting treatment but may plateau or

even decrease after 1 year. Weight gain is linked to a decreased metabolic rate, increased calorie intake, and decreased physical activity (Weinsier et al., 1998; Baptista, 1999), although it is not yet known by which precise mechanisms it is induced by atypical antipsychotics.

The consequences of excessive weight gain (obesity) associated with antipsychotic drugs are likely to include poor compliance or even discontinuation of therapy by the patients. Poor adherence almost always leads to relapse and a worsened long-term outcome (Bernstein, 1987; Fenton et al., 1997). As obesity is frequently a comorbid condition with schizophrenia (Allison et al., 1999b), schizophrenic patients are inherently at increased risk of developing obesity-related conditions such as cardiovascular disease and type II diabetes (Mukherjee et al., 1996; Nasrallah, 2000). Particular consideration should therefore be given to the choice of antipsychotic drugs in this patient population with regard to weight change as a potential serious adverse health effect.

This review examines the limited evidence regarding the mechanism of weight gain with antipsychotic drugs and then focuses on the differential effects of atypical antipsychotics on weight. In the majority of the studies discussed, weight gain was assessed for each patient by calculating the difference between body mass index (BMI) at the start and end of treatment. BMI describes relative weight for height and is a widely accepted measure of weight change and classification (WHO, 1998). It is calculated as the weight in kilograms divided by the square of the height in meters. Optimal BMI is between 20 and 25, while 25–30 is regarded as 'overweight' and >30 as 'obese'.

2. Mechanisms of weight gain with atypical antipsychotics

It is generally believed that there are multiple mechanisms by which antipsychotic drugs induce weight gain but their precise nature remains unknown. Weight gain as a drug effect may be a multifactorial process, involving serotonergic, histaminergic, and/or adrenergic neurotransmission (Baptista, 1999). Atypical antipsychotics achieve their therapeutic effects by modulating the activity of these neural pathways. Weight gain as a side effect may be due to the blockade of certain receptors, e.g. 5-HT_{2c}, that modulate appetite and body weight (Stanton, 1995). The ratios between various receptor affinities may also be important. As the atypical antipsychotics vary in their receptor affinity profiles, it would be expected that they differ in their tendency to cause weight gain.

The specific interaction between antipsychotic drugs and hormones (such as insulin and leptin) that regulate appetite and obesity has yet to be fully elucidated. Melkersson et al. (2000) found that olanzapine therapy was associated with increased levels of insulin and leptin, as well as with weight gain. Leptin regulates food uptake and energy expenditure; it is synthesized by fat cells and its serum levels correlate positively with BMI (Kraus et al., 1999). An increase in serum leptin levels has been associated with olanzapine and clozapine therapy (Brömel et al., 1998; Kraus et al., 1999). This increase may be a direct effect of the antipsychotics on the feedback

mechanism for this hormone or an effect of the increased appetite, impaired satiety, and weight gain associated with the antipsychotic drugs.

3. Clozapine

Clozapine is associated with some of the largest weight gains seen with any antipsychotic drug (Stanton, 1995; Sussman and Ginsberg, 1999). Cohen et al. (1990) reported a mean weight gain of 11.2 kg for six patients taking clozapine at maximum doses of 175–600 mg/day for a mean duration of 6.5 months. Included in this group was one patient who had substantial weight gain of 31.3 kg while taking clozapine at a maximum dose of 400 mg/day for 9 months. It should be noted that a gain of >7% of the ideal body weight is considered a health risk. This amounts to about 4 kg for an average woman and 6 kg for an average man.

Leadbetter et al. (1992) reported a mean weight gain of 6.3 kg (9% increase in body weight) in 21 patients over 16 weeks of treatment. Eight (38%) patients experienced marked weight gains (>10% of their body weight). Lamberti et al. (1992) reported a mean weight gain of 7.7 kg for 36 patients receiving a mean clozapine dose of 380 mg/day over 6 months. This increase represented 11% of the patients' maximum ideal weight. Twenty-seven (75%) of the patients gained at least 4.5 kg and 15 (42%) patients gained at least 9 kg.

In a retrospective study of 82 patients treated with clozapine 500–600 mg/day for up to 90 months, Umbricht et al. (1994) found that about 50% of patients became substantially overweight (≥20%). Patients who were underweight at baseline had significantly higher percentage weight increases than those with ideal weight and those who were overweight. The cumulative incidence rates were >80% of patients for a 10% weight gain and 38% of patients for a 20% weight gain. Weight gain occurred mostly within the first year but continued into the third year.

Frankenburg et al. (1998) found significant mean increases (5.9 and 3.3 kg/m^2 in female and male patients, respectively) in BMI among 42 patients receiving clozapine over a 3-year period. The final BMI appeared to be dependent on the baseline BMI and the dose of clozapine.

Finally Reinstein et al. (1999) reported significant weight loss (mean 4.2 kg; range 0.45–18.6 kg over 10 months) with the addition of quetiapine to the treatment regimen of 65 patients who had previously been on clozapine monotherapy. Furthermore, they reported a significant improvement in glycemic control in three (20%) of 13 patients who developed diabetes during clozapine monotherapy.

4. Olanzapine

Olanzapine is associated with significant weight gain with a magnitude comparable to that produced by clozapine (Jibson and Tandon, 1998). Nemeroff (1997) reviewed the safety and efficacy data from four clinical trials in which olanzapine was compared with placebo and/or haloperidol in nearly 3000 patients. Olanzapine patients

had a dose-related increase in weight, achieving after 1 year a mean weight gain of approximately 12 kg with a high dose (12.5–17.5 mg/day), compared with a mean weight gain of 3 kg with a low dose (1 mg/day) (Fig. 1) (Nemeroff, 1997). Weight gain was greatest for patients who had a starting dose of 12.5–17.5 mg/day of olanzapine and/or were underweight (as indicated by BMI) at the start of the study.

Beasley (1997) reported that 41% of a total of 1455 patients receiving olanzapine in four combined studies experienced a clinically significant (≥7%) weight gain. The incidence of weight gain was highest (32%) among patients who were underweight at baseline and lowest (11%) among those who were overweight. Most weight gain occurred during the first 6–8 weeks of therapy and reached a plateau by the end of the first year. Further evidence of olanzapine-associated weight gain provided by Weiden et al. (1996) showed that after >6 weeks of olanzapine treatment, one-third of the patients reported weight gain as the 'most problematic' side effect. Weight gain occurred in most of the 15 patients and was regarded as a serious problem for 3/15 (20%) patients.

In addition, a study of nine patients with schizophrenia showed that 16 months of treatment with olanzapine was associated with a rise in triglyceride levels and mean weight gain of 10 kg (Sheitman et al., 1999). The rise in triglyceride levels is an important factor for some patients because of its link with an increased risk for coronary artery disease. Finally, a recent study of olanzapine with or without fluoxetine in treatment-resistant depression reported a weight gain of 6.07 kg with olanzapine alone over 8 weeks (Shelton et al., 2001). It may be that patients with mood disorders are especially susceptible to weight gain with olanzapine.

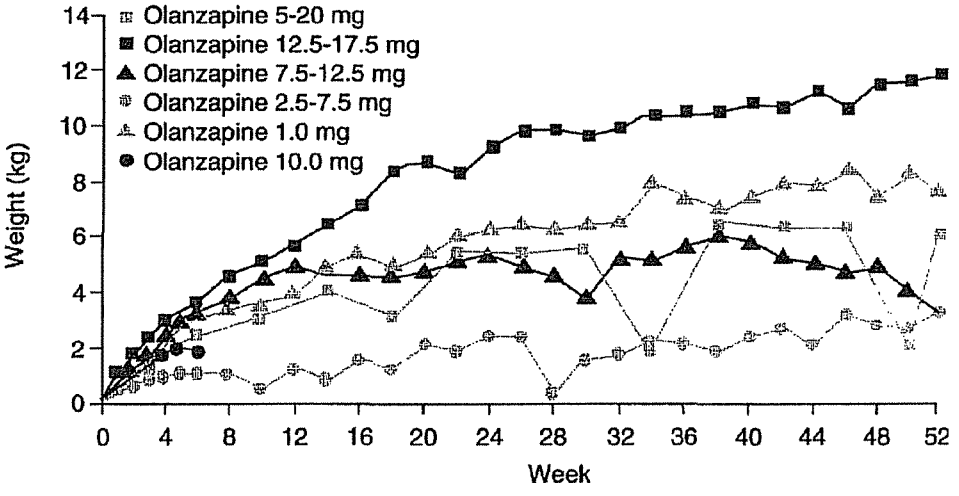


Fig. 1. Mean change in weight over time at different olanzapine dosages. Data from four different studies combined. Olanzapine dosages were as follows: Study 1—fixed at 1 and 10 mg/day; Study 2—flexible within three dose ranges (2.5–7.5, 7.5–12.5, and 12.5–17.5 mg/day); Study 3—as Study 2 with the addition of a fixed dose of 1 mg/day; and Study 4—flexible within the range 5–20 mg/day. Adapted from Nemeroff (1997). Copyright 1997, Physicians Postgraduate Press. Reprinted by permission.

5. Risperidone

Risperidone is associated with modest weight gain that is not dose related. The literature reveals consistent values for weight gain with risperidone therapy. Claus et al. (1992) reported a mean weight gain of 2 kg after 12 weeks of treatment with risperidone at a mean final dose of 12 mg/day. Owens (1994) reported mean weight gains of 1–2 kg after 8 weeks of treatment with risperidone at 2–16 mg/day.

A mean weight gain of 2.8 kg occurred after 8 weeks of treatment in 11 patients randomized to 2, 6, 10, or 16 mg/day risperidone. The change in weight from baseline was statistically significant, as was the difference in weight change between the risperidone and placebo groups. There was no significant correlation between weight gain and risperidone dose or plasma concentration (Anderson et al., 1993). Brecher and Geller (1997) reported an average weight gain of 2.6 kg among 1200 patients treated for a mean duration of 213 days (30 weeks) in long-term risperidone trials.

A recent study comparing risperidone and haloperidol over 1 year showed a mean weight gain of 2.3 kg in the risperidone group and a decrease of 0.73 kg in the haloperidol group (Csernansky et al., 2002).

6. Ziprasidone

Ziprasidone has been associated with minimal weight loss, minimal weight gain, or no effect on weight. A pooled analysis of four short-term (4–6 week) studies showed the proportion of patients who experienced weight gain exceeding 7% body weight was significantly greater in those treated with ziprasidone (dose range 10–200 mg/day) compared with placebo (10 versus 4%) (Geodon (ziprasidone HCl) Prescribing Information, 2001). The same analysis indicated that the overall incidence of anorexia adverse events with ziprasidone was low (2 versus 1% placebo) but was reported to be dose related.

In a randomized, placebo-controlled, double-blind study, Arato et al. (1999) assessed ziprasidone in 219 chronic schizophrenia patients for 1 year, at three dose levels (40, 80, and 160 mg/day). Patients in this study were carefully monitored, being either in hospital or in sheltered accommodation with continuous medical or nursing supervision. Ziprasidone was not associated with weight gain but it remains to be established whether these results will replicate in patients managed in an unsupervised outpatient setting.

In a head-to-head, double-blind, 6-week, randomized trial, ziprasidone was associated with a small increase in weight (n = 116, 0.93 kg, 0.24 kg/m^2) that was significantly lower than with olanzapine (n = 120, 3.57 kg, 1.17 kg/m^2) (Simpson et al., 2001). However, the incidence of gastrointestinal-related adverse events such as dyspepsia (11.8 versus 7.5%) and nausea (10.3 versus 6.0%) was higher amongst patients receiving ziprasidone than those receiving olanzapine and the extent to which this may have affected food intake and weight change is not known.

Results from various studies of these four atypical antipsychotics (clozapine, olanzapine, risperidone, and ziprasidone) were included in a meta-analysis by Allison et

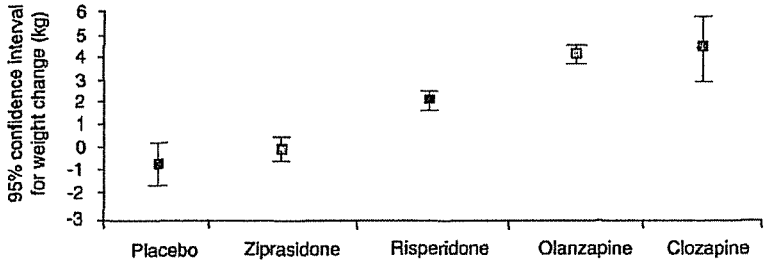


Fig. 2. Mean weight change with 95% confidence intervals after 10 weeks on standard drug doses. Adapted from Allison et al. (1999a). Copyright 1999, American Psychiatric Association; http://ajp.psychiatryonline.org. Reprinted by permission.

al. (1999a). The mean weight change was estimated after 10 weeks of treatment with antipsychotic drugs at a standard dose (Fig. 2) (Allison et al., 1999a). The results, with substantial weight gain for clozapine and olanzapine, modest weight gain for risperidone, and negligible weight gain for ziprasidone, were consistent with previous reports as described above.

7. Quetiapine

Results from several clinical trials have shown that short-term quetiapine treatment is associated with modest weight gain that is not dose related. The effects on weight are neutral when quetiapine is used as long-term monotherapy.

A total of 2216 patients who had participated in controlled, uncontrolled, and open-label extension trials were included in an analysis of weight change in long-term (12 months) quetiapine treatment (Jones et al., 2000; Rak et al., 2000). Analysis of the overall data showed a small mean weight increase of 2.08 kg (n = 778) over the first 5–6 weeks of treatment (Table 1) and no dose-related weight gain (Table 2). Over longer treatment periods, the increases from baseline showed little change (Table 1) and remained unrelated to dose (Table 2). The mean dose of quetiapine at 9–12 months was 428 mg/day. An analysis of weight change by BMI categories at baseline revealed a trend for greater weight gain in patients with low baseline

Table 1
Mean weight change from baseline in patients treated with quetiapine during controlled, uncontrolled, and open-label extension trials; data from Rak et al. (2000)

Duration of treatment	No. of patients	Mean weight change, kg (+SE)
5–6 weeks	778	2.08 (0.15)
9–10 weeks	171	2.16 (0.46)
6–9 months	556	1.85 (0.48)
9–12 months	360	2.77 (0.56)

Table 2
Mean weight change in patients receiving different quetiapine doses during controlled, uncontrolled, and open-label extension trials; adapted from Jones et al. (2000)

Dose (mg)	Mean weight change (kg)	
	5–6 weeks of treatment	9–12 months of treatment
<125	1.21	1.78
125–225	2.95	1.38
>225–450	2.13	3.83
>450–675	1.95	2.26
>675	2.05	2.13

BMIs (<23) than in patients with normal (23–27) or high (>27) baseline BMIs. Only one patient withdrew from treatment because of weight gain. It should be noted that most of the patients included in this analysis had participated in studies in which antipsychotics other than quetiapine were allowed. It is therefore difficult to attribute weight gain specifically to quetiapine or the other antipsychotics or a combination of both.

The absence of a dose-related weight gain is consistent with the results of an earlier double-blind, dose-ranging study in which 361 patients received quetiapine for up to 6 weeks and in which no apparent relationship was found between weight change and dose (Arvanitis and Miller, 1997; Jones et al., 2000). A separate analysis included patients from controlled, uncontrolled, and open-label extension trials in which quetiapine was the only antipsychotic permitted (Brecher et al., 2000; Brecher and Melvin, 2001). A total of 427 patients received a mean dose of 475 mg/day after 1 year of open-label quetiapine treatment. There was minimal weight gain over an 80-week period (Fig. 3) (Brecher et al., 2000).

Quetiapine had no overall effect on weight across the baseline BMI range. The relationship between weight change and BMI was examined in a subset of 178 patients who had received quetiapine for at least 26 weeks (mean duration of 18.6 months) at a mean final dose of 473 mg/day. Patients were categorized according to their baseline BMIs (<18.5 = underweight; 18.5 to <25 = normal weight; 25 to <30 = overweight; 30 to <35 = obese; and ≥35 = severely obese). Small numbers of patients in some of these categories resulted in wide 95% confidence intervals associated with the mean weight change from baseline. Fig. 4 shows that the 95% confidence intervals of the mean weight change from baseline included zero when all BMI groups were considered together and individually (with the exception of the severely obese) (Brecher et al., 2000). These results indicate an absence of weight effect across the BMI range with long-term quetiapine treatment except in severely obese patients, where quetiapine was associated with a statistically significant decrease in weight. The effect of quetiapine was not related to dose or gender. Fig. 5 shows weight changes by dose group, using the modal dose value for the last recorded weight (endpoint) value (Brecher et al., 2000). There were no statistically significant changes from baseline in mean weight. The 95% confidence intervals of

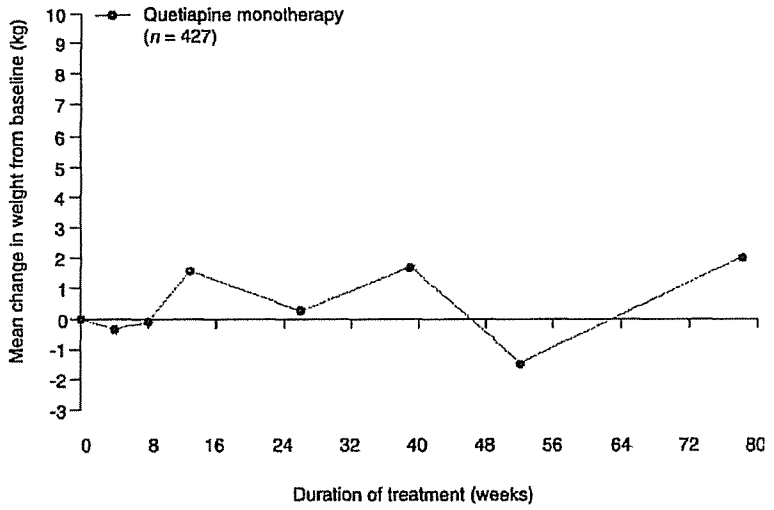


Fig. 3. Mean weight change from baseline during quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

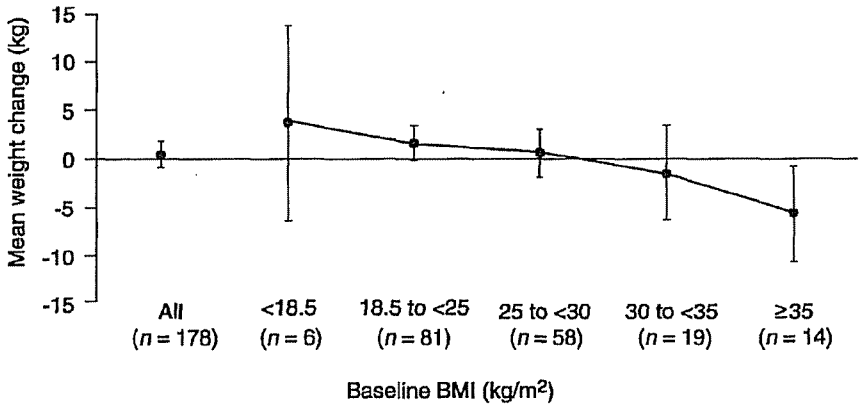
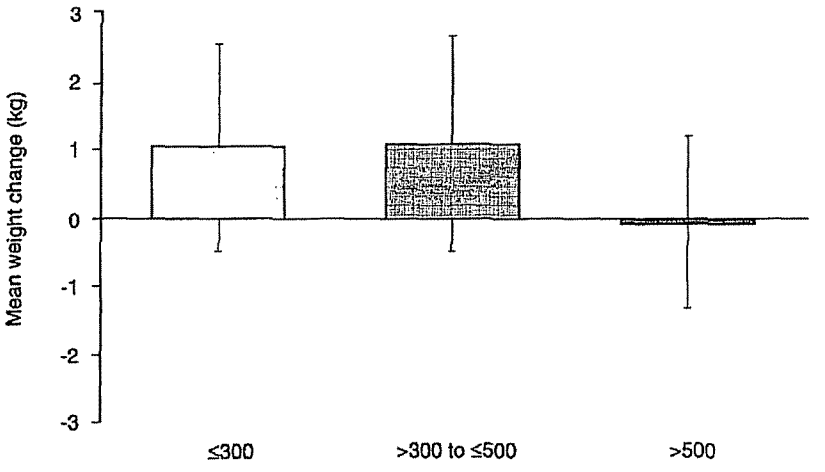


Fig. 4. Mean weight change with 95% confidence intervals from baseline to endpoint by baseline category in patients receiving quetiapine monotherapy for at least 6 months. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

the mean weight change from baseline included zero for all three dose groups, indicating that the effect of quetiapine on patient weight was neutral across the dose range. There was also no correlation between increasing dose and mean long-term weight changes.

These studies cumulatively suggest that quetipine is associated with only minimal weight changes during short-term use which are not dose related and do not increase over time. Further, given the chronic nature of maintenance antipsychotic therapy, the long-term effect of quetiapine on weight change appears to be neutral overall and potentially weight normalizing in some obese patients.



Mean duration of treatment (days)	343	407	327
No. patients	103	94	174

Fig. 5. Mean weight change with 95% confidence intervals from baseline to endpoint by modal daily dose at endpoint in patients receiving quetiapine monotherapy. Adapted from Brecher et al. (2000). Copyright Martin Dunitz, reprinted by permission.

8. Discussion

Weight gain can be a serious iatrogenic health problem in patients with schizophrenia and other psychoses. It is an important side effect of antipsychotic medication and may have adverse implications for adherence with long-term antipsychotic therapy. Excessive weight gain may also lead to other adverse health effects, e.g. type II diabetes, hyperlipidemia, and cardiovascular disease. Weight gain occurs to varying extents depending on the drug.

In the atypical class of antipsychotics, clozapine and olanzapine are associated with the most significant weight gain. Risperidone is associated with modest weight changes that are not dose related. Ziprasidone has a relatively low risk of weight gain during short-term treatment and no overall weight gain during long-term treatment in patients under continuous clinical supervision.

Quetiapine is associated with modest short-term weight changes that do not increase over time and are not dose related. The overall effect of quetiapine on weight in long-term treatment is neutral, with some weight loss in severely obese patients. Quetiapine has favorable efficacy and tolerability profiles, which have resulted in high levels of patient satisfaction and the normalization of eating habits

in 73% of the study population (Hellewell et al., 1999). Hence, the available data suggest that quetiapine has a favorable benefit:risk profile. Taking into account both the minimal weight change and placebo-level EPS across the full dose range, quetiapine should be considered as a first-choice antipsychotic in the long-term treatment of schizophrenia.

While high BMI and obesity are well-known risk factors for diabetes and are associated with insulin resistance, more recently some of the atypical antipsychotics have themselves been linked to impaired glucose metabolism and diabetes mellitus (see supplement Sussman, 2001, for review of this area). Because patients with psychosis (schizophrenia and mania) have an increased risk for comorbid diabetes even before antipsychotic pharmacotherapy is initiated (Mukherjee et al., 1996; Cassidy et al., 1999), it can be difficult to determine a causal link between atypical antipsychotic-induced diabetes, antipsychotic exacerbation of pre-existing diabetes, or the development of diabetes as a comorbidity of the psychotic disorder itself. However, while there have been no definitive well-controlled and randomized trials, there is some evidence from case reports in the literature that clozapine (Koval et al., 1994; Popli et al., 1997) and olanzapine (Wirshing et al., 1999; Goldstein et al., 1999) may impair glucose metabolism and increase the risk of diabetes in patients with schizophrenia (Henderson, 2002). Interestingly in another recent study, Newcomer et al. (2002) found that glucose levels were significantly elevated in nondiabetic schizophrenia patients treated with clozapine and olanzapine but not in those treated with risperidone or typical agents.

In conclusion, the differential weight gain of various atypicals should be considered in the selection of a first-line antipsychotic, given the potentially serious health effects of obesity. However, other adverse events such as dose-dependent EPS (Jibson and Tandon, 1998), hyperprolactinemia-induced sexual dysfunction (Turrone et al., 2002), and cardiac conduction effects (Glassman and Bigger, 2001) should also be taken into consideration in the selection of a first-line atypical antipsychotic. By minimizing adverse effects, patient adherence to long-term treatment of psychotic disorders is substantially increased.

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EXHIBIT 32

Weight and Diabetes Sell Sheet VM 08 15 05 v6

Hello, this is Christine Ney, Scientific Alignment Manager for Seroquel I want to follow-up with you on the Weight and Diabetes Sell Sheet you received recently This selling tool contains data on both weight gain and diabetes that you'll find helpful as you engage customers about SEROQUEL's tolerability -- and address their comments and questions on these issues

First, you'll notice that key data and summary statements (even footnotes!) are presented clearly in this compact, two-sided format Then, you'll notice the message points that help you focus and organize your thoughts with facts like

- Overall weight gain for SEROQUEL-treated patients diagnosed with schizophrenia was 2 3 kg after at least 26 weeks of treatment

You can also point out that

- In monotherapy bipolar mania trials, the average weight gain was 1 8 kg In adjunct therapy bipolar mania trials, the average gain was 1 97 kg

And

- In pivotal trials (of 3- to 12-week duration), with "weight gain" defined as an increase of 7% or more from baseline, the incidence was 13% to 23% in patients receiving SEROQUEL, versus 4% to 7% in patients on placebo

- There were no discontinuations due to weight gain with SEROQUEL in pivotal trials for schizophrenia and bipolar mania

For Diabetes consider pointing out that

- Seroquel has over 8 million patient exposures worldwide since it was approved for use in 1997 While hyperglycemia-related adverse events have been reported in patients taking atypical antipsychotics, including SEROQUEL, to date the available data has not established a causal link between diabetes and SEROQUEL

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL

Our objective is to neutralize customer objections to SEROQUEL's weight and diabetes profile This is possible with messages that are supported by data -- the kind of message you can take away from the Weight and Diabetes Sell Sheet

I think you'll appreciate the potential of this tool Then, don't forget to refocus the call on SEROQUEL's Trusted Tolerability profile, highlighting the low incidence of Akathisia and EPS with SEROQUEL

Thanks everyone and good selling!

EXHIBIT 34

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

James L. Gaskill, PharmD
Director
Promotional Regulatory Affairs
AstraZeneca
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Mailstop D1C-715
Wilmington, DE 19803-8355
Fax (302) 886-2822

RE: NDA # 20-639
Seroquel® (quetiapine fumarate) Tablets
MACMIS ID # 14670

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (238110) for Seroquel® (quetiapine fumarate) tablets (Seroquel) submitted by AstraZeneca under cover of Form FDA 2253. This piece is false or misleading because it minimizes the risk of hyperglycemia and diabetes mellitus and fails to communicate important information regarding neuroleptic malignant syndrome, tardive dyskinesia, and the bolded cataracts precaution. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i). The promotional material raises significant public health and safety concerns through its minimization of the risks associated with Seroquel.

Background

According to its FDA-approved product labeling (PI), Seroquel is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex and for the treatment of schizophrenia.

The PI includes important warnings and precautions. It states (in pertinent part):

WARNINGS

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical

manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing

a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

Orthostatic Hypotension
SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. SEROQUEL should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

Cataracts
Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures
As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

* * *

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, FDA asked all manufacturers of atypical antipsychotics to include a warning in their PI regarding this risk on September 11, 2003. FDA believes that the safe use of Seroquel can be enhanced by informing prescribers and patients about these events and increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment and thus reduce the risk for the most serious outcomes. The PI including the hyperglycemia and diabetes mellitus warning for Seroquel was approved on January 12, 2004.

Misleading Presentation

Page two of the professional sales aid starts with a prominent header, which states "Diabetes Information," and then presents the following five bullets:

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

The first two bullets contain information from the Warning in Seroquel's PI regarding Hyperglycemia and Diabetes Mellitus concerning the observed hyperglycemic events and the areas of uncertainty about the glucose abnormality findings. While the agency acknowledges that it has not been established whether Seroquel causes diabetes, you fail to include information regarding the increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. The increased risk may be due to confounding factors and is not completely understood, but a warning about it was recently added to Seroquel's PI to enhance the safe use of Seroquel and protect public health. Because your bullets about the relationship between the use of Seroquel and hyperglycemia leave out this information, the bullets are misleading and undermine the warning.

Furthermore, the fourth bullet claims that the percentage of diabetes or diabetes-related events in post-marketing reports is "very rare (<0.01%) with Seroquel." In light of the voluntary nature of post-marketing adverse event reporting by healthcare professionals and patients, it is infeasible to obtain an accurate percentage of all diabetes or diabetes-related

adverse events associated with Seroquel based upon these reports. Therefore, quantifying post-marketing adverse events in this manner is misleading.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the professional sales aid fails to include relevant risk information about the Warnings and Precautions that it presents. While the professional sales aid states that "Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia," it fails to reveal that the risk of developing the condition and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered increase. The sales aid also fails to mention that the syndrome may partially or completely remit if antipsychotic treatment is withdrawn. Additionally, the professional sales aid states that "A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL." This statement is misleading in that it fails to reveal that NMS is a potentially fatal symptom complex associated with the administration of Seroquel. Furthermore, the professional sales aid fails to convey the important information from the PI regarding the clinical manifestations of NMS and that management of NMS should include immediate discontinuation of antipsychotic drugs.

The professional sales aid states that "Precautions include the risk of seizures, orthostatic hypotension, and cataract development." This statement is misleading because it omits material facts from the PI about these risks. In particular, it fails to mention important information from the bolded cataracts precaution recommending that physicians examine all patients at initiation of Seroquel treatment or shortly thereafter, and at six month intervals during chronic treatment, to detect cataract formation.

Conclusion and Requested Action

For the reasons discussed above, the professional sales aid misbrands Seroquel in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i).

DDMAC requests that AstraZeneca immediately cease the dissemination of violative promotional materials for Seroquel such as those described above. Please submit a written response to this letter on or before November 30, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Seroquel the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14670 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seroquel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Dean
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EXHIBIT 35

Nolvadex—Cont.

NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3–5 days of beginning NOLVADEX and cleared within 2–5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20–40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the EBCTCG 1990 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for two years or longer than in those that used tamoxifen for less than two years. There was no indication that doses greater than 20 mg per day were more effective. In B-14, the NSABP adjuvant study in women with node-negative breast cancer, one 10 mg NOLVADEX tablet was given twice a day for at least five years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see CLINICAL PHARMACOLOGY). The optimal duration of adjuvant NOLVADEX therapy remains to be determined.

HOW SUPPLIED

10 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. NDC 0310-0600.

20 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets. NDC 0310-0604.

Store at controlled room temperature, 20–25° C (68–77° F) [see USP]. Dispense in a well-closed, light-resistant container.

ZENECA Pharmaceuticals
A Business Unit of ZENECA Inc.
Wilmington, DE 19850-5437 USA
SIC 64130-00 Rev S 02/98

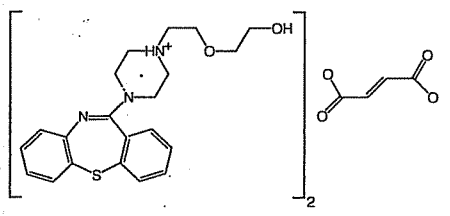
Shown in Product Identification Guide, page 346

SEROQUEL® ℞

[serō-quĕl]
(quetiapine fumarate)
tablets

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo*[b,f]*[1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2{\cdot}C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow) and 200 mg (white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain; serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}= 1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL. SEROQUEL'S antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL'S antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro,* quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose and was recovered in the urine and feces, respectively. Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10–30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed. (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6, and 3A4.

Quetiapine oral clearance is induced by the prototype cytochrome P450 3A4 inducer, phenytoin. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin (See **DRUG INTERACTIONS** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium, or lorazepam. (See **DRUG INTERACTIONS** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the management of the manifestations of psychotic disorders was established in 3 short-term (6-week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600, and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score, with the maximum effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose of SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS. Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of SEROQUEL was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects

)QUEL for extended periods should periodically
:he long-term usefulness of the drug for the in-
ıtient (See **DOSAGE AND ADMINISTRA-**

NDICATIONS

L is contraindicated in individuals with a known
ivity to this medication or any of its ingredients.

:S

: Malignant Syndrome (NMS)

ly fatal symptom complex sometimes referred to
ptic Malignant Syndrome (NMS) has been re-
ıssociation with administration of antipsychotic
possible cases of NMS [2/2387 (0.1%)] have been
ı clinical trials with SEROQUEL. Clinical mani-
of NMS are hyperpyrexia, muscle rigidity, altered
tus, and evidence of autonomic instability (irreg-
or blood pressure, tachycardia, diaphoresis, and
srhythmia). Additional signs may include ele-
tinine phosphokinase, myoglobinuria (rhabdomy-
d acute renal failure.

ostic evaluation of patients with this syndrome is
d. In arriving at a diagnosis, it is important to
ses where the clinical presentation includes both
edical illness (e.g., pneumonia, systemic infection,
ıntreated or inadequately treated extrapyramidal
symptoms (EPS). Other important considerations
erential diagnosis include central anticholinergic
eat stroke, drug fever, and primary central ner-
em (CNS) pathology.

ıgement of NMS should include: 1) immediate dis-
ion of antipsychotic drugs and other drugs not es-
ı concurrent therapy; 2) intensive symptomatic
: and medical monitoring; and 3) treatment of any
ant serious medical problems for which specific
ts are available. There is no general agreement
ecific pharmacological treatment regimens for

nt requires antipsychotic drug treatment after re-
ım NMS, the potential reintroduction of drug ther-
ld be carefully considered. The patient should be
monitored since recurrences of NMS have been re-

)yskinesia

ıme of potentially irreversible, involuntary, dyski-
vements may develop in patients treated with an-
ic drugs. Although the prevalence of the syndrome
to be highest among the elderly, especially elderly
it is impossible to rely upon prevalence estimates to
at the inception of antipsychotic treatment, which
are likely to develop the syndrome. Whether anti-
c drug products differ in their potential to cause tar-
kinesia is unknown.

of developing tradive dyskinesia and the likelihood
will become irreversible are believed to increase as
ıtion of treatment and the total cumulative dose of
:hotic drugs administered to the patient increase.
r, the syndrome can develop, although much less
ıly, after relatively brief treatment periods at low

s no known treatment for established cases of tar-
skinesia, although the syndrome may remit, par-
r completely, if antipsychotic treatment is with-
Antipsychotic treatment, itself, however, may sup-
r partially suppress) the signs and symptoms of the
ne and thereby may possibly mask the underlying
. The effect that symptomatic suppression has upon
g-term course of the syndrome is unknown.

these considerations, SEROQUEL should be pre-
in a manner that is most likely to minimize the oc-
:e of tardive dyskinesia. Chronic antipsychotic treat-
hould generally be reserved for patients who appear
r from a chronic illness that (1) is known to respond
ipsychotic drugs, and (2) for whom alternative,
effective, but potentially less harmful treatments
available or appropriate. In patients who do require
treatment, the smallest dose and the shortest dura-
treatment producing a satisfactory clinical response
be sought. The need for continued treatment should
ssessed periodically.

s and symptoms of tardive dyskinesia appear in a pa-
n SEROQUEL, drug discontinuation should be con-
d. However, some patients may require treatment
EROQUEL despite the presence of the syndrome.

!AUTIONS

al

static Hypotension: SEROQUEL may induce ortho-
hypotension associated with dizziness, tachycardia
ı some patients, syncope, especially during the initial
itration period, probably reflecting its α_1-adrenergic
onist properties. Syncope was reported in 1% (22/
of the patients treated with SEROQUEL, compared
)% (0/206) on placebo and about 0.5% (2/420) on active
)l drugs. The risk of orthostatic hypotension and syn-
nay be minimized by limiting the initial dose to 25 mg
ee **DOSAGE AND ADMINISTRATION**). If hypoten-
sion occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to defect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range that was apparent early on during treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, but about 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient, and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to prestudy levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal and Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3–5 day period of initial dose titration, and also at times of reinitiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3–5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a noninducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Continued on next page

Seroquel—Cont.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Although data are not available from clinical studies, caution is indicated when SEROQUEL is administered with a potent enzyme inhibitor of cytochrome P450 3A (e.g., ketoconazole, itraconzaole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs:

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (one a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/kg) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the result of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women, and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients. (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time of worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% of SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded in the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

[See table 1 at bottom of next page]

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness of EPS associated with SEROQUEL treatment. Three methods were used to measure EPS (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapydramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

[See table at bottom of next page]

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS, and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinical important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- 6-week-placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

dverse Events Observed During the Premarketing on of SEROQUEL

ıg is a list of COSTART terms that reflect treatıergent adverse events as defined in the introducıe ADVERSE REACTIONS section reported by paeated with SEROQUEL at multiple doses ≥ 75 mg/ ing any phase of a trial within the premarketing ıe of approximately 2200 patients. All reported ıre included except those already listed in Table 1 or re in labeling, those events for which a drug cause ıote, and those event terms which were so general as ıinformative. It is important to emphasize that, althe events reported occurred during treatment with UEL, they were not necessarily caused by it.

are further categorized by body system and listed in f decreasing frequency according to the following ons: frequent adverse events are those occurring in ; 1/100 patients (only those not already listed in the ed results from placebo-controlled trials appear in ting); infrequent adverse events are those occurring 0 to 1/1000 patients; rare events are those occurring r than 1/1000 patients.

ıs System: ***Frequent:*** hypertonia, dysarthria; ***Infre-*** abnormal dreams, dyskinesia, thinking abnormal, dyskinesia, vertigo, involuntary movements, confumnesia, psychosis, hallucinations, hyperkinesia, licreased* urinary retention, incoordination, paranoid n, abnormal gait, myoclonus, delusions, manic reacpathy, ataxia, depersonalization, stupor, bruxism, cat- reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal me, choreoathetosis, delirium, emotional lability, eu-, libido decreased*, neuralgia, stuttering, subdural oma.

as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** ain, pelvic pain*, suicide attempt, malaise, photosen- reaction, chills face edema, moniliasis; ***Rare:*** abdonlarged.

tive System: ***Frequent:*** anorexia; ***Infrequent:*** ıd salivation, increased appetite, gamma glutamyl ıeptidase increased, gingivitis, dysphagia, flatulence, ıenteritis, gastritis, hemorrhoids, stomatitis, thirst, caries, fecal incontinence, gastroesophageal reflux, ıemorrhage, mouth ulceration, rectal hemorrhage, e edema; ***Rare:*** glossitis, hematemesis, intestinal obion, melena, pancreatitis.

ovascular System: ***Frequent:*** palitation; ***Infrequent:*** ilatation, QT interval prolonged, migraine, bradycarerebral ischemia, irregular pulse, T wave abnormality, ıe branch block, cerebrovascular accidenct, deep ıbophlebitis, T wave inversion; ***Rare:*** angina pectoris, fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL® (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25–50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1–2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25–50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400–500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, in patients with hepatic impairment, and in patients who are debilitated or who had a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital. (See Drug Interactions under **PRECAUTIONS**)

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required, and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to SEROQUEL.

Continued on next page

Table 1. Treatment-Emergent Adverse Experience
Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

System/ rred Term	SEROQUEL (n=510)	Placebo (n=206)
as a Whole		
.dache	19%	18%
ıenia	4%	3%
.ominal pain	3%	1%
k pain	2%	1%
er	2%	1%
ous System		
ınolence	18%	11%
ziness	10%	4%
stive System		
ıstipation	9%	5%
Mouth	7%	3%
;pepsia	6%	2%
liovascular System		
;tural hypotension	7%	2%
:hycardia	7%	5%
abolic and Nutritional Disorders		
ight gain	2%	0%
ı and Appendages		
sh	4%	3%
ɔiratory System		
initis	3%	1%
cial Senses		
r pain	1%	0%

vents for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the llowing: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, ıyalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, ry skin, amblyopia, and urinary tract infection.

e Groups	Placebo	SEROQUEL 75 mg	150 mg	300 mg	600 mg	750 mg
kinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
S incidence	16%	6%	6%	4%	8%	6%
icholinergic edications	14%	11%	10%	8%	12%	11%

Seroquel—Cont.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
Store at 25°C (77°F) excursions permitted to 15–30°C (59–86°F). [See USP]

ANIMAL TOXICOLOGY

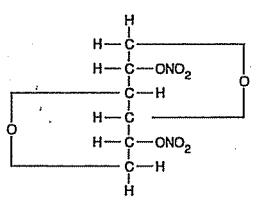
Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10–250 mg/kg in rats, 75–750 mg/kg in mice; these doses are 0.1–3.0, and 0.1–4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.
In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.
Manufactured by:
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5347
64122-00 Rev C 11/97
Shown in Product Identification Guide, page 346

SORBITRATE®

[*sorb 'i-trate*]
(Isosorbide Dinitrate)

DESCRIPTION

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins.
Isosorbide dinitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of 70°C and has an optical rotation of +134° (c = 1.0, alcohol, 20°C). Isosorbide dinitrate is freely soluble in organic solvents such as acetone, alcohol, and ether; but is only sparingly soluble in water.
SORBITRATE is available as:

SORBITRATE® CHEWABLE TABLETS USP
5 mg Chewable Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, confectioner's sugar, corn starch, flavor, hydrogenated vegetable oil, magnesium stearate, mannitol, povidone, Yellow 10.
SORBITRATE® ORAL TABLETS USP
5 mg Oral Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
10 mg Oral Tablet. Each tablet contains 10 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
20 mg Oral Tablet. Each tablet contains 20 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
30 mg Oral Tablet. Each tablet contains 30 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
40 mg Oral Tablet. Each tablet contains 40 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.

CLINICAL PHARMACOLOGY

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.
Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.
Pharmacokinetics: Once absorbed, the distribution volume of isosorbide dinitrate is 2–4 L/kg, and this volume is cleared at the rate of 2–4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is effected primarily by denitration to the 2-mononitrate (15%–25%) and the 5-mononitrate (75%–85%).
Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.
The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10–12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (eg, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.
Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had *less* exercise tolerance at the end of the daily dose-free interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.
Bioavailability of ISDN after single sublingual doses is 40%–50%. Multiple-dose studies of sublingual ISDN pharmacokinetics have not been reported; multiple-dose studies of ingested ISDN have observed progressive increases in bioavailability during chronic therapy. Serum levels of ISDN reach their maxima 10–15 minutes after sublingual dosing.
Absorption of isosorbide dinitrate after oral dosing is nearly complete, but bioavailability is highly varible (10%–90%), with extensive first-pass metabolism in the liver. Serum levels reach their maxima about an hour after ingestion. The average bioavailability of ISDN is about 25%; most studies have observed progressive increases in bioavailability during chronic therapy.
The absorption kinetics of chewable isosorbide dinitrate tablets have not been studied. Absorption of ingested ISDN is known to be nearly complete, although bioavailability is highly variable. Ingested ISDN undergoes extensive first-pass metabolism in the liver; it is not known what portion of this first-pass effect is avoided by buccal absorption of the chewable formulation.
Kinetic studies of absorption of immediate-release formulations of ISDN have found highly variable bioavailability with extensive first-pass metabolism in the liver. Most such studies have observed progressive increases in bioavailability during chronic therapy.
Clinical Trials: In a controlled trial in which 0.4 mg of sublingual nitroglycerin took 1.9 minutes to begin to produce an anti-anginal effect, 5 mg of sublingual ISDN took 3.4 minutes to begin to produce a similar effect. In the same trial, the anti-anginal effect of the sublingual nitrogylcerin was evident for about an hour, while that of the sublingual ISDN lasted about 2 hours.
In other controlled trials, the anti-anginal efficacy of sublingual ISDN has persisted for periods ranging from 30 minutes up to 4 hours.
Multiple-dose trials of sublingual ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using sublingual ISDN is not known.
In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.
Controlled trials of single oral doses of isosorbide dinitrate have demonstrated effective reductions in exercise-related angina for up to 8 hours. Anti-anginal activity is present about 1 hour after dosing.
Most controlled trials of multiple-dose oral ISDN taken every 12 hours (or more frequently) for several weeks have shown statistically significant anti-anginal efficacy for only 2 hours after dosing. Once-daily regimens, and regimens with at least one daily interval of at least 14 hours (eg, a regimen providing doses at 0800, 1400 and 1800) have shown efficacy after the first dose of each day that was similar to that shown in the single-dose studies cited above.
In controlled trials in which sublingual nitroglycerin took $1^1/_2$–2 minutes to begin to produce an anti-anginal effect, chewable ISDN tablets took $2^1/_2$–3 minutes to begin to produce a similar effect. In these same trials, the anti-anginal effect of sublingual nitroglycerin was evident for about 1–$1^1/_2$ hours, while that of chewable ISDN lasted about an hour longer.
Clinical trials of chewable ISDN have used doses of 5 and 10 mg. It is not known whether lower doses would be equally effective.
Multiple-dose trials of chewable ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using chewable ISDN is, because of the rapid onset of action of this formulation, probably somewhat longer.
From large, well-controlled studies of other nitrates, it is reasonable to believe that the maximal achievable daily duration of anti-anginal effect from isosorbide dinitrate is about 12 hours. No dosing regimen for isosorbide dinitrate has, however, ever actually been shown to achieve this duration of effect. In the absence of data from multiple-dose trials, and considering the capacity of organic nitrates to induce tolerance, it is not reasonable to assume that multiple sublingual ISDN tablets taken during the course of a day will all have similar effects.

INDICATIONS AND USAGE

SORBITRATE sublingual tablets and chewable tablets are indicated for the prevention and treatment of angina pectoris due to coronary artery disease. However, because the onset of action of these tablets is significantly slower than that of sublingual nitroglycerin, they are not the drug of first choice for abortion of an acute anginal episode.
SORBITRATE oral tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of immediate release oral isosorbide dinitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide dinitrate is contraindicated in patients who are allergic to it or other nitrates.

WARNINGS

The benefits of isosorbide dinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitor-

must be used to avoid the hazards of hypotension and ıycardia. Because the effects of oral and chewable ISDN ıets are so difficult to terminate rapidly, this formulation ot recommended in these settings.

ECAUTIONS

ıeral: Severe hypotension, particularly with upright ture, may occur with even small doses of isosorbide dini- te. This drug should therefore be used with caution in ients who may be volume depleted or who, for whatever son (eg, diuretics), are already hypotensive. Hypotension uced by isosorbide dinitrate may be accompanied by par- ıxical bradycardia and increased angina pectoris.

rate therapy may aggravate the angina caused by hyper- phic cardiomyopathy.

tolerance to isosorbide dinitrate develops, the effect of ɔlingual nitroglycerin on exercise tolerance, allthough ll observable, is somewhat blunted.

industrial workers who have had long-term exposure to known (presumably high) doses of organic nitrates, toler- ce clearly occurs. Chest pain, acute myocardial infarction, d even sudden death have occurred during temporary thdrawal of nitrates from these workers, demonstrating e existence of true physical dependence.

me clinical trials in angina patients have provided nitro- rcerin for about 12 continuous hours of every 24-hour day. uring the daily dose-free intervals in some of these trials, ginal attacks have been more easily provoked than before eatment, and patients have demonstrated hemodynamic bound and decreased exercise tolerance. The importance these observations to the routine, clinical use of isosor- de dinitrate is not known. It may be prudent to gradually thdraw patients from ISDN when the therapy is being rminated, rather than stopping the drug abruptly.

formation for Patients: Patients should be told that the ıti-anginal efficacy of isosorbide dinitrate is strongly re- ted to its dosing regimen, so the prescribed schedule of ɔsing should be followed carefully. In particular, daily eadaches sometimes accompany treatment with isosorbide nitrate. In patients who get these headaches, the head- :hes are a marker of the activity of the drug. Patients ıould resist the temptation to avoid headaches by altering ıe schedule of their treatment with isosorbide dinitrate, nce loss of headache may be associated with simultaneous ıss of anti-anginal efficacy. Aspirin and/or acetaminophen, n the other hand, often successfully relieve isosorbide dini- ate-induced headaches with no deleterious effect on iso- ɔrbide dinitrate's anti-anginal efficacy.

reatment with isosorbide dinitrate may be associated with ghtheadedness on standing, especially just after rising rom a recumbent or seated position. This effect may be ıore frequent in patients who have also consumed alcohol.

)RUG INTERACTIONS

The vasodilating effects of isosorbide dinitrate may be addi- ive with those of other vasodilators. Alcohol, in particular, ıas been found to exhibit additive effects of this variety.

SDN acts directly on vascular smooth muscle; therefore, ıy other agent that acts on vascular smooth muscle can be xpected to have decreased or increased effect depending on he agents.

Marked symptomatic, orthostatic hypotension has been re- ɔorted when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class ɔf agents may be necessary.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of isosorbide dinitrate. In a modified two-litter reproduction study, there was no remarkable gross pathology and no altered fertility or gestation among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day.

Pregnancy: Pregnancy Category C: At oral doses 35 and 150 times the maximum recommended human daily dose, isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits. There are no adequate, well-controlled studies in pregnant women. Isosorbide dinitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether isosorbide dinitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide dinitrate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to isosorbide dinitrate are generally dose-related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator. Headache, which may be severe and persistent, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Cutaneous vasodilation with flushing may occur. Transient episodes of lightheadedness, dizziness, and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. (See OVERDOSAGE.)

Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred. (See OVERDOSAGE.)

Data are not available to allow estimation of the frequency of adverse reactions during treatment with SORBITRATE tablets.

OVERDOSAGE

Hemodynamic Effects: The ill effects of isosorbide dinitrate overdose are generally the results of isosorbide dinitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of the following: persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); initial hyperpnea; air hunger; and dyspnea, later followed by slow breathing and/or reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of isosorbide dinitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide dinitrate overdose.

There are no data suggesting what dose of isosorbide dinitrate is likely to be life-threatening in humans. In rats, the median acute lethal dose (LD_{50}) was found to be 1100 mg/kg (approximately 500 times the recommended therapeutic dose in humans).

No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide dinitrate and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of isosorbide dinitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide dinitrate overdose. Because the hypotension associated with isosorbide dinitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs and passive movement of extremities may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide dinitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8–6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

As noted above (**CLINICAL PHARMACOLOGY**), multiple studies with ISDN and other nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. Every dosing regimen for ISDN must provide a daily dose-free interval to minimize the development of this tolerance. To achieve the necessary nitrate-free interval with immediate-release oral ISDN, it appears that at least one of the daily dose-free intervals must be at least 14 hours long. In the case of sublingual and chewable tablets, it is probably true that one of the daily dose-free intervals must be somewhat longer than 14 hours.

As also noted above (**CLINICAL PHARMACOLOGY**), the effects of the second and later doses have been smaller and shorter-lasting than the effects of the first.

Large controlled studies with other nitrates suggest that no dosing regimen with SORBITRATE Tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

A patient anticipating activity likely to cause angina should take one SORBITRATE Chewable Tablet, 5 mg, about 15 minutes before the activity is expected to begin. SORBITRATE Sublingual Tablet, 2.5 mg to 5 mg, may be used to abort an acute anginal episode, but this use is recommended only in patients who fail to respond to sublingual nitroglycerin.

In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.

As with all titratable drugs, it is important to administer the minimum dose that produces the desired effect. The usual starting dose of SORBITRATE Oral Tablets is 5 mg to 20 mg, two or three times daily. For maintenance therapy, 10 mg to 40 mg, two to three times daily is recommended. Some patients may require higher doses. A daily dose-free interval of at least 14 hours is advisable to minimize tolerance. The optimal interval will vary with the individual patient, dose and regimen.

HOW SUPPLIED

SORBITRATE®Chewable Tablets USP

5 mg Chewable Tablets. (NDC-0310-0810) Green, round, scored tablets (identified front "S", reverse "810") are supplied in bottles of 100 and 500.

SORBITRATE Oral Tablets USP

5 mg Oral Tablets. (NDC-0310-0770) Green, oval-shaped, scored tablets (identified front "S", reverse "770") are supplied in bottles of 100 and 500 and Unit Dose 100.

10 mg Oral Tablets. (NDC-0310-0780) Yellow, oval-shaped, scored tablets (identified front "S", reverse "780") are supplied in bottles of 100, 500 and Unit Dose 100.

20 mg Oral Tablets. (NDC-0310-0820) Blue, oval-shaped, scored tablets (identified front "S", reverse "820") are supplied in bottles of 100 and Unit Dose 100.

30 mg Oral Tablets. (NDC-0310-0773) White, oval-shaped, scored tablets (identified front "S", reverse "773") are supplied in bottles of 100 and Unit Dose 100.

40 mg Oral Tablets. (NDC-0310-0774) Light Blue, oval-shaped, scored tablets (identified front "S", reverse "774") are supplied in bottles of 100 and Unit Dose 100.

Avoid storage at temperatures above 25°C (77°F).

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, DE 19850-5437

Rev P 02/98 SIC No. 64119-00

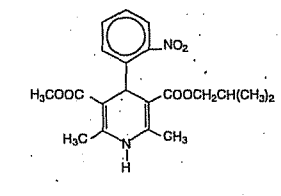
Shown in Product Identification Guide, page 346

SULAR®

(Nisoldipine)
Extended Release Tablets
For Oral Use

DESCRIPTION

SULAR® (nisoldipine) is an extended release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. Nisoldipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester, $C_{20}H_{24}N_2O_6$, and has the structural formula:



Nisoldipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 388.4. SULAR tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow release formulation and the core as a fast release formulation. SULAR tablets contain either 10, 20, 30 or 40 mg of nisoldipine for once-a-day oral administration.

Continued on next page

EXHIBIT 36

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639

2003/494
Seroquel
NDA 20-639

AstraZeneca Pharmaceuticals
Attention: Gerald L. Limp
Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp

Please refer to your new drug application (NDA) for Seroquel (quetiapine fumarate) Tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Seroquel can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

WARNINGS
Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are

starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/11/03 03:12:47 PM

EXHIBIT 37

AstraZeneca

Date: OCT 1 5 2003

Russell G. Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-120, Room 4049
1451 Rockville Pike
Rockville, MD 20852-1448

Re: NDA 20-639
SEROQUEL® (quetiapine fumarate) Tablets
Response to FDA Request for Labeling Change

Dear Dr. Katz:

The purpose of this submission is to acknowledge receipt of the September 11, 2003 correspondence from the Division of Neuropharmacological Drug Products which requests changes be made to the SEROQUEL label regarding the use of atypical antipsychotic medications and diabetes mellitus.

Earlier this summer, as part of our normal operating procedure, AstraZeneca completed a comprehensive internal analysis of existing data and concluded that the available data do not establish a causal link between diabetes and Seroquel. Among other things, our analysis is consistent with the Food and Drug Administration's position concerning the prevalence of diabetes in the general and schizophrenic populations. Moreover, we believe that the association between diabetes and schizophrenia further confounds the evaluation and interpretation of post-marketing reports and retrospective epidemiology studies that are already confounded by other factors such as lifestyle, weight, family history and other medications.

AstraZeneca is committed to working closely with the FDA to ensure that physicians receive accurate information to assist them in the appropriate prescribing of Seroquel. Currently, we are in the process of evaluating steps to address the concerns raised in the September 11, 2003 correspondence. Prior to taking any actions with respect to changing the Seroquel label, we would like to discuss such steps with the agency and ask that a meeting be scheduled in the first half of December 2003. I will be in contact with Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager in the near future to arrange such a meeting.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19850-8355

regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Brian Abbott, Regulatory Project Manager, at (302) 886-1437.

Sincerely,

Kevin McKenna, Ph.D.
Executive Director, Regulatory Affairs
Telephone: (302) 886-2742
Fax: (302) 886-3342

Technical Review Jacket: Steven D. Hardeman, RPh, HFD-120, Room 4028

EXHIBIT 38

AstraZeneca

IMPORTANT DRUG INFORMATION

April 22, 2004

Dear Health Care Provider,

In 2003, the Food and Drug Administration (FDA) asked all manufacturers of atypical antipsychotic medications, including AstraZeneca Pharmaceuticals LP (AstraZeneca), to add a Warnings statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL® (quetiapine fumarate) Tablets. AstraZeneca added the FDA Warnings statement to its SEROQUEL Prescribing Information and communicated that change to you in a letter dated January 30, 2004.

It has come to the attention of AstraZeneca that the Warnings statement set forth in its January 30, 2004 letter did not quote in its entirety the new Warnings statement included in the Prescribing Information; the words "and periodically during treatment" were omitted from the end of the second sentence of the second paragraph of the warning. Accordingly, enclosed is a new letter dated April 22, 2004, which quotes the Warnings statement from the Prescribing Information in its entirety.

Please discard the January 30, 2004 letter and replace it with the enclosed letter.

Sincerely,

W. Macfadden MD

Wayne Macfadden, MD
US Medical Director, SEROQUEL

219669

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437

Tel 302 886 3000
www.astrazeneca-us.com

AZPH1001 (01/00)

AstraZeneca

IMPORTANT DRUG INFORMATION

April 22, 2004

Dear Health Care Provider,

AstraZeneca Pharmaceuticals LP would like to inform you of important labeling changes regarding SEROQUEL® (quetiapine fumarate). The FDA has asked all manufacturers of atypical antipsychotic medications, including AstraZeneca, to add a Warnings statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL. Accordingly, the SEROQUEL Prescribing Information has been updated with the addition of the following information:

WARNINGS

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437
Tel 302 886 3000
www.astrazeneca-us.com

AstraZeneca remains committed to providing you with the most current product information available for the management of your patients. You may immediately review the Warnings statement about hyperglycemia and diabetes mellitus in the SEROQUEL Prescribing Information by visiting the web site at www.Seroquel.com. Updated package inserts containing the additional hyperglycemia and diabetes mellitus information will accompany the medication in the near future and you should, of course, refer to the insert for full Prescribing Information.

As always, we request that serious adverse events be reported to AstraZeneca at 1-800-236-9933 or to the FDA MedWatch program at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or by e-mail at www.fda.gov/medwatch. For additional medical information about SEROQUEL, please call 1-800-236-9933 from 9:00 am to 5:00 pm EST, Monday through Friday.

Sincerely,

Wayne Macfadden, MD
US Medical Director, SEROQUEL

219669

EXHIBIT 39

AstraZeneca

Minutes

Chairman
Vikram Dev - VP and Head of CDS US

Date 08 June 2007

Page 1/2

Participants
Eileen Carey - SERM Manager
Barry Arnold – EU Qualified Person
Judy Zander - Ex Dir US Safety Surveillance
Leigh Jefferies – GDSP Seroquel IR
Ron Leong - TASL
Martin Brecher – MSD
Julia Manning – Legal
Eileen Ming – Epidemiology
Liza DeAnnuntis – GDSP Seroquel XR
Xiang Ni – DS Physician
Susanne Fors – GRAD
Kathryn Bradley – AD Regulatory Labeling
Lisa Boomazian – Surveillance
Eva Alam – Surveillance
Linda Warner – Surveillance
Nina Delillio – Surveillance
Tara Lee – Surveillance
Howard Hutchinson - CMO
Ihor Rak – VP Clin TA – NS
Sandi Raff – Sr Dir Clin Res
Kurt Engelman – Stat Sci Dir
Kevin Stansberry – Med Com
Kevin McKenna – Reg TA VP – NS
Jan Eriksson – Dis Med/Epi
Mikael Astrom – Stat Sci Dir
Henrik Andersson – Biostats
Kevin Carroll – Chief Statistical Expert
Hakan Revevtlid – Clin Sci
Bjorn Paulsson – Med Neuro Sci
Anders F Karlsson – Dis Med/Epi
Kristina Axe – Med Com

Secretary
Eileen Carey – SERM Manager

Apologies:
Michelle Dillone – Legal
Nina Sherak – Surveillance
Deborah Rolfe – Surveillance
Richard Hellmund – CIS
Janet Spiers-Alston – Global SERM Manager
Joachim Forsgren – VP CDS
Robert Williams – SERM Support
Stacy Forbes – SERM Administrator

Meeting date
08 June 2007

Location
Wilmington

Subject
SERM – Seroquel

Confidential

1. Glucose Dysregulation

Following a review of all clinical trial data, including studies D1447C00125, D1447C00126, and D1447C00127, epidemiology literature, and post-marketing data, SERM recommended adding the following to Section 4.4 Special warnings and special precautions for use:

> **Increases in Blood Glucose and Hyperglycemia**
> Increases in blood glucose and hyperglycemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see also section 4.8 Undesirable effects).

AstraZeneca
Mereside
Alderley Park
Macclesfield
Cheshire
SK10 4TG

Tel: +44 (0) 1625 582828
Fax: +44 (0) 1625 583074
www.astrazeneca.com

SERM also recommended adding the following to Section 4.8 Undesirable Effects.

Frequency	System Organ Class	Event
Common (≥1% - <10 %)	Investigations	Blood glucose increased to hyperglycaemic level*

***Footnote**
Fasting blood glucose ≥126 mg/dL or a non fasting blood glucose ≥200 mg/dL on at least one occasion.

ACTION: Surveillance (Lisa Boornazian) and Medical Communications (Kevin Stansberry) will write the Clinical Overview.
Priority: B
Signal Source: Internal
Number of Signals: 1
Clinical Overview author(s): Kevin Stansberry and Lisa Boornazian
Due date for readiness of draft CO: 13 June 2007
Core Data Sheet (CDS) author: Kathryn Bradley
Due date for CDS issue: 15 June 2007
Due date for Investigators Brochure issue: 31 July 2007

EXHIBIT 4

Unknown

From: Murray Michael MF
Sent: Thursday, March 23, 2000 11:55 AM
To: Jones Martin AM - PHMS
Cc: Mullen Jamie JA; Goldstein Jeffrey JM; Tumas John JA
Subject: HELP FW: Meta Analyses

Importance: High

Attachments: RE: Meta Analyses; RE: Meta Analyses; TD0004.doc; TD0005 version 2.doc

RE: Meta Analyses

Martin,
I think we need your help on this one. Can you please read the attached messages. Can me, you, Jeff, and Jamie discuss this in Paris. I don't understand why we got such vast differences in these anayses.
Thanks,
Mike

Mike Murray

Senior Product Strategist, SEROQUEL
1-800-456-3669 ext. 4328
michael.murray@astrazeneca.com

From: Tumas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

Here's the analyses that I got from Emma. I've also attached a message that I sent to her yesterday asking for clarification.

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo **and** haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own analysis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or telelconference) and discuss where to go from here. We need to do this quickly, because Schulz needs to get a draft ready for APA and he needs any additional analyses we can give him well before then.

Thanks,

John

RE: Meta Analyses

From: Westhead Emma EK
Sent: Wednesday, March 22, 2000 12:44 PM
To: Tumas John JA
Cc: Shadwell Pamela PG
Subject: RE: Meta Analyses

Hi John,

Some of the work you need has already been completed within the Commercial Support Team. I attach the relevant technical documents for your information.

TD0004.doc (94 KB) TD0005 version 2.doc (127 KB)

I've tried to summarise below our current position with this data:

CGI

- Meta-Analysis has been done by CST vs haloperidol (TD005). No superiority of Seroquel over haloperidol was seen - although we can claim we are 'as least as effective' as haloperidol'.
- Seroquel vs placebo. A meta-analysis has not been performed, this could be progessed with the CST.

BPRS

- Meta-analysis has been performed on BPRS total, anxiety item, factor I, factor V, hostility item, hostility cluster and mood cluster for those patients who were symptomatic at baseline (TD004). No superiority of Seroquel over haloperidol was seen - although we can claim we are 'as least as effective' as haloperidol'.
- A similar meta-analysis was performed vs placebo on the same items. Superiority of Seroquel over placebo was seen in this case.

SANS

- A meta-analysis of SANS scores has been done for placebo and is contained within the new promotional guide (available for the Handover). Superiority of Seroquel over placebo.
- I don't believe many haloperidol studies actually recorded SANS but will check this.

Hence, for the BPRS analysis we haven't covered all of the items suggested by Dr Schulz. However, given that we are seeing a consistent picture of similar efficacy to haloperidol, I don't think we would seen anything different when analysing the other individual items. It depends on your focus - would you be happy to state "as least as effective" as haloperidol.

I propose that we could progress the following:

- a meta-analysis of CGI, seroquel vs placebo
- consider wether SANS data was recorded in haloperidol studies
- Discuss with Dr Schulz the focus of the meta-analysis of BPRS/CGI vs haloperidol before any extra work is done to look at items not yet analysed.

Could you consider these proposals and also let me know what your exact deadline is? I'll need to feed this in against the current work being progressed within the CST.

Kind Regards - sorry for the lengthy reply!
Emma

From: Tumas John JA
Sent: 22 March 2000 15:42
To: Westhead Emma EK
Subject: FW: Meta Analyses

Hi Emma,

It seems that Martin will not be easy to reach during the next week or so. Do you have a feel for how doable the below is? Dr. Schulz is supposed to have a draft manuscript for us by APA in May and I expect he will need the below in order to do so.

Thanks,

John

From: Tumas John JA
Sent: Monday, March 20, 2000 1:39 PM
To: Jones Martin AM - PHMS
Cc: Westhead Emma EK; Goldstein Jeffrey JM; Gavin Jim JP
Subject: Meta Analyses

Dear Martin,

You may be aware that Jeff and I met with Drs. Shulz and Tandon in Chicago a couple of weeks ago to discuss a few review manuscripts. The one with Dr. Schulz was conceived as a result of the responder meta analyses that were used for his APA (and CPNP) abstracts. After formulating an outline for the manuscript, Dr. Shulz put together a list of other meta analyses that would be needed in order for him to progress the manuscript. Below is a list of additional analyses Dr. Schulz has requested. Could you let me know the feasibility of these requests?

I've attached a first draft of the poster for CPNP that I sent to Dr. Schulz.

Best regards,

John

Meta analyses comparing quetiapine to haloperidol and placebo:

1) Total BPRS
2) CGI
3) BPRS Factor scores, ie thought disorder, anxiety, depression, negative symptoms.
4) Individual BPRS items: hallucinatory behavior, suspiciousness, flattened affect.
5) SANS
6) Control for factors:
    a) age
    b) gender
    c) length of illness.

<<File: Schulz.doc>>

EXHIBIT 40

AstraZeneca

Date: 22 June 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry
5901-B Ammendale Road
Beltsville, MD 20705-12666

RE: NDA 20-639 and NDA 22-047
SEROQUEL® (quetiapine fumarate) Tablets
Supplement-Changes Being Effected in 30 Days

Dear Sir/Madam:

In accordance with 21 CFR 314.70, AstraZeneca Pharmaceuticals LP (AstraZeneca) is submitting a Changes Being Effected in 30 Days labeling supplement for SEROQUEL (quetiapine fumarate) Tablets, NDA 20-639. AstraZeneca would also like to apply the changes in this submission to SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets, NDA 22-047. The labeling is being updated due to a review of clinical trial data.

The data included in the updated label provide new information on SEROQUEL and hyperglycemia. The data presented are from three sources. Glucose data were examined from 1) two long-term trials investigating treatment with SEROQUEL and a mood stabilizer to maintain an effect in patients with bipolar disorder; 2) a 6-month trial in schizophrenic patients designed to specifically examine atypical therapy and glucose metabolism; and 3) the pooling of placebo-controlled trials where duration of SEROQUEL therapy was less than 12 weeks.

The 2 long-term trials of SEROQUEL are D1447C00126, entitled "A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients" and Trial D1447C00127, entitled "A Multicenter, Randomized, Parellel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Divalproex) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients" . These trials will be submitted as part of a supplemental NDA application in July 2007.

The 6 month trial D1441C00125, which was previously submitted to the Agency, is entitled "A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine, and Risperidone in the Treatment of Patients with Schizophrenia".

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

The data from the pooled placebo-controlled trials has been submitted to FDA previously in several different applications.

AstraZeneca is also requesting a teleconference approximately 5-7 days before the 30-day review expires.

Changes to the labeling appear in the following sections:

WARNINGS, Hyperglycemia and Diabetes Mellitus: A cross reference to the ADVERSE REACTIONS, Hyperglycemia sub-section has been added.

ADVERSE REACTIONS, Laboratory Changes, a new sub-section under the heading "Hyperglycemia" has been added.

The following files have been included in this submission:

1. SEROQUEL Labeling History-outstanding labeling supplements that may affect the review of this Special Supplement-Changes Being Effected (CBE) Supplement.

2. SEROQUEL Labeling Text-annotated and non-annotated versions of the Final Printed Labeling, which reflect changes noted in the CBE.

3. Structured Product Labeling-The final printed labeling in SPL format

4. Supporting documentation- Glucose Dysregulation in Patients treated with SEROQUEL (quetiapine)

This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 20June07. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, AstraZeneca is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Gerald Limp, Director at (302) 886-8017.

Sincerely,

Kathryn Bradley, Associate Director
Regulatory Affairs
Telephone: (302) 886-5622
Fax: (302) 886-3342

EXHIBIT 41

Rev: 10/07 SIC 30417-03

SEROQUEL

(quetiapine fumarate)

TABLETS

RX ONLY

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

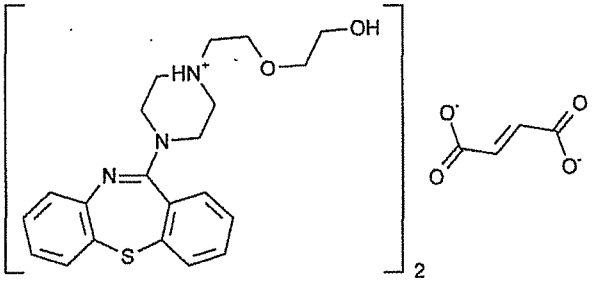
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SEROQUEL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SEROQUEL is not approved for use in pediatric patients. (See Warnings:

Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

SEROQUEL® (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.
Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg and 400 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and

adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, is unknown. However, it has been proposed that the efficacy of SEROQUEL in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.
SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn,

neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed

typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See Drug Interactions under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Disorder

Depression

The efficacy of SEROQUEL for the treatment of depressive episodes associated with bipolar disorder was established in 2 identical 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale with scores ranging from 0 to 60. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score. Improvement in symptoms, as measured by change in MADRS score relative

to placebo, was seen in both studies at Day 8 (week 1) and onwards. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS $\geq$ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an

adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the

BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

2. In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Disorder

SEROQUEL is indicated for the treatment of both:

- depressive episodes associated with bipolar disorder
- acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.

Depression

The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients (See **CLINICAL PHARMACOLOGY**). Effectiveness has not

been systematically evaluated in clinical trials for more than 8 weeks.

Mania

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy.

The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in

	Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are

experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine

phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel (see **ADVERSE REACTIONS, Hyperglycemia**). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Leukopenia, Neutropenia and Agranulocytosis: In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related

to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue SEROQUEL and have their WBC followed until recovery (See ADVERSE REACTIONS).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free

thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥240 mg/dL and triglycerides ≥200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have

shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo.

Potential for Cognitive and Motor Impairment:
Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are

reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo, (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%).

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and

Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**).

Withdrawal

Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including SEROQUEL. Gradual withdrawal is advised.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families

and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Leukopenia/Neutropenia:

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL.

Laboratory Tests

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors. **(see PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum

plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of

other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25

to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use: Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that

might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories.

In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events

for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse events for bipolar depression.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo- Controlled Trials

Bipolar Disorder:

Depression: Overall, discontinuations due to adverse events were 12.3% for SEROQUEL 300 mg vs 19.0% for SEROQUEL 600 mg and 5.2% for placebo.

Mania: Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials.

Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/ Preferred Term	**SEROQUEL (n=719)**	**PLACEBO (n=404)**
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%

Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with

SEROQUEL was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%),

postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 8-weeks) of bipolar depression in 5% or more of patients treated with SEROQUEL (doses of 300 and 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 4. Treatment-Emergent Adverse Experience Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression

Body System/ Preferred Term	**SEROQUEL (n=698)**	**PLACEBO (n=347)**
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Nervous System Disorders		
Sedation	30%	8%
Somnolence	28%	7%
Dizziness	18%	7%
Lethargy	5%	2%
Respiratory, Thoracic, and Mediastinal		

Disorders		
Nasal Congestion	5%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

SEROQUEL

Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct

therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

In placebo controlled monotherapy clinical trials involving 3368 patients on SEROQUEL and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $<1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with SEROQUEL, compared to 0.1% (2/1349) in patients treated with placebo. **(See PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis)**

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed.

Hyperglycemia

In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo.

In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥200 mg/dl was 1.7% and the incidence of a

fasting treatment-emergent blood glucose level ≥ 126mg/dl was 2.6%.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 2 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the

tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase

increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: *Frequent:* sweating; *Infrequent:* pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.
*adjusted for gender

Post Marketing Experience:
Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, and restless legs..
Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic

hormone secretion (SIADH), and Stevens-Johnson Syndrome (SJS).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (**See PRECAUTIONS: Orthostatic Hypotension**) One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

Management of Overdosage:

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative

should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Bipolar Disorder

Depression

Usual Dose: SEROQUEL should be administered once daily at bedtime to reach 300 mg/day by day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
SEROQUEL	50 mg	100 mg	200 mg	300 mg

In the clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for days 1-4 respectively. Patients receiving 600 mg increased to 400 mg on day 5 and 600 mg on day 8 (Week 1). Antidepressant efficacy was demonstrated with SEROQUEL at both 300 mg and 600 mg however, no additional benefit was seen in the 600 mg group.

Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in bid doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in bid divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of

25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one

side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

50 mg Tablets (NDC 0310-0278) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '50' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

400 mg Tablets (NDC 0310-0279) yellow, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '400' on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

• Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
• Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
• Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:
• thoughts about suicide or dying
• attempts to commit suicide
• new or worse depression
• new or worse anxiety
• feeling very agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse irritability
• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?
• **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it.
Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

SEROQUEL is a trademark of the AstraZeneca group of companies

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA
Rev. 10/07 SIC 30417-03

EXHIBIT 42

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-639/S-036
NDA 22-047/S-001

AstraZeneca Pharmaceuticals LP
Attention: Gerald Limp
Director, Regulatory Affairs
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Dear Mr. Limp:

We acknowledge receipt of your supplemental new drug applications dated June 22, 2007, and July 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets (NDA 20-639) and Seroquel XR (quetiapine fumarate) extended-release tablets (NDA 22-047).

We additionally refer to an Agency letter dated January 8, 2008, requesting information on glucose abnormalities.

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

20-639/S-036 dated June 22, 2007
- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.

22-047/S-001 dated July 25, 2007
- Revisions throughout labeling to provide for new information on quetiapine and hyperglycemia.
- Revisions to the **Adverse Reactions**-Postmarketing Experience section.
- Revisions to the **Drug Interactions**-P450 3A Inhibitors section.

We have completed our review of these supplemental applications, and they are approvable.

In general, the revisions made to the Postmarketing Experience and Drug Interactions sections are acceptable, and these comments were conveyed to you in an Agency letter dated May 13, 2008.

However, we are requesting the following changes to your proposed labeling (double underline font denotes additions and strike through font denotes deletions) before we can take a final action on these supplemental applications.

> *In 2 long-term placebo-controlled randomized withdrawal clinical trials, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dl) ~~for patients more than 8 hours since a meal~~ was 18.0 per 100 patient years for SEROQUEL (10.7% of patients)*

and 9.5 for placebo per 100 patient years (4.6% of patients). The mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo. Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of SEROQUEL on blood glucose may be underestimated.

For the 2 long term placebo-controlled bipolar maintenance trials, we are deleting the statement "more than 8 hours since a meal" from the proposed labeling language. In general, it does indicate fasting, but you indicated that there was still the possibility of caloric intake in the form of liquids or snacks. Therefore, since these subjects may not have been in a fasting state, this phrase should be deleted to reduce confusion.

Since the 2 long-term placebo-controlled bipolar maintenance trials studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with Seroquel and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥126 mg/dl or a non fasting blood glucose ≥200 mg/dl was 3.5% for quetiapine and 2.1% for placebo. The mean increase in glucose from baseline was 2.70 mg/dl for SEROQUEL and 1.06 mg/dl for placebo.

For the 24 week active-controlled trial designed to evaluate glycemic status, you included only the LS mean data, and not the mean change from baseline to week 24 for the quetiapine group. Please provide us these data so that it can be incorporated into product labeling.

Based on the PLR regulations, your proposed addition of "Adverse Reactions, Vital Signs and Laboratory Studies, Hyperglycemia (6.2)" under RECENT MAJOR CHANGES in the Highlights should be deleted.

Additionally, we would refer you to our January 8, 2008 letter requesting information on the following glucose data. Please submit these information by the requested due date, June 30, 2008.

- Glucose mean and median change analyses of serum glucose levels by baseline values (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data)
- Fasting serum glucose post-treatment cut-off values are 140 mg/dL, 200 mg/dL, and 300 mg/dL
- Non-fasting serum glucose post-treatment cut-off value level is 300 mg/dL
- Observed case analyses of mean glucose change for the following specified exposure durations - 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks
- Analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%

- Analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
6/25/2008 04:03:23 PM

EXHIBIT 43

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

DECLARATION OF WILLIAM C. WIRSHING, M.D.

1. My name is William C. Wirshing, M.D. I am competent to make this declaration and the facts stated herein are within my personal knowledge and are true and correct.

2. I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectric systems). I received my M.D. from the University of California at Los Angeles in 1982, graduating with a 3.97 G.P.A. and receiving the Sandoz Awared for "Excellence in the Behavioral Sciences." I remained at UCLA for both my rotating internship, during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency was at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia.

3. I am the Vice-President in charge of research and continuing medical education for Exodus Inc. in Culver City, California and also Clinical Director of Exodus Real Recovery in Agoura Hills, California. In my clinical psychiatric practice, I see approximately 325 new patients in a typical month; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students.

4. Over the decades between 1986 and 2006, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. I have attached my curriculum vitae and the report I submitted to counsel for Plaintiffs in this litigation as Exhibits A and B respectively, and I incorporate those documents by reference herein.

5. In my 25-plus years of clinical and research experience, I have had countless, significant, and frequent opportunities to read, review, and apply to my clinical practice with patients the information contained on FDA-approved prescription medicine labels/package inserts. I am particularly familiar with the warnings and other labeling information accompanying a class of antipsychotic medications commonly referred to as second generation antipsychotics such as risperidone ("Risperdal"), olanzapine ("Zyprexa"), ziprasidone ("Geodon"), aripiprazole ("Abilify"), and quetiapine (Seroquel).

6. With particular respect to Seroquel's 1997-to-present label concerning weight gain, it is my opinion that, rather than adequately "warn" about the 23%-33% or higher risk

of statistically significant weight gain that AstraZeneca observed in clinical trials of Seroquel, the company obscured and buried the weight gain data and, more importantly, the effect of the data by putting it in the "adverse reaction" section of the label. AstraZeneca has never "warned" about weight gain because the necessary information concerning weight gain is not clearly stated in the "warnings" section of the label. As a practicing clinician, it is unclear, ambiguous, and misleading to prescribing doctors for the single most prominent serious toxic characteristic of this drug (statistically significant weight gain) not to be included in the "warnings" section of the label where a prescribing physician would expect to find such information. The "adverse reactions" section on the package insert is near the end of the labeling, very often several dozen paragraphs following the "warnings" section, and is akin to a laundry list. In practice, it is quite simply not given the same attention or priority by prescribers as the "warnings" and "precautions" sections near the beginning of the label. Therefore, the warning given regarding weight gain is inadequate. As shown by the true and correct copy of the Physicians' Desk Reference section on Seroquel from 2004, attached as Exhibit C, the highlighted weight gain information is dwarfed by the overwhelming balance of other information about the drug.

7. The 1997-to-present Seroquel label is also unclear, inaccurate, and misleading because weight gains of the magnitude that Seroquel causes, according to its own label and the company's data, are impressively large and impact an amazingly large and consistent percentage of patients. The serious and frequently deadly health consequences associated with weight gain (namely hyperglycemia and diabetes mellitus, and complications therefrom) necessitated adequate warning. Such warning should have appeared in the "warnings" not

"adverse reactions" section of the label. Placement of the weight gain clinical trials data in the "adverse reactions" section inadequately conveys to prescribing physicians the severity of the health consequences associated with a 23%-33% or more weight increase associated with Seroquel treatment, further rendering the inclusion of such data in the adverse reactions section inadequate. Additionally, the label fails to describe any of the health consequences for which weight gain creates an increased risk—i.e., hyperglycemia and diabetes mellitus, among other serious and potentially lethal health concerns including increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). To put it another way, the labeling fails to state a "cause and effect" relationship between the statistically significant weight gain accompanying Seroquel use and the increase in glucose dysregulation that was also revealed by AstraZeneca's clinical trials and company data that I have reviewed.

8. Regarding AstraZeneca's marketing materials during this same period with respect to weight gain, as well as sales representatives' direct messages (discussions) to physicians, the materials that I have reviewed, including Doctor Brecher's 2000 article and Doctor Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or had favorable weight profiles. Sales materials profiling patient experiences with Seroquel by a Doctor Reinstein, which I have reviewed, implied that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. Further, despite information identifying weight gain as a dose-dependent side effect, AstraZeneca has repeatedly stated in its sponsored literature and marketing material that I reviewed (e.g., the Brecher and Nasrallah

articles) that there is no dose-dependent relationship between Seroquel and weight gain Other marketing messages included claims that Seroquel is "weight neutral" or causes "minimal weight gain," further obscuring and diluting the severity of any mention of clinically significant weight gain in the label's adverse reaction section. At best, such promotional messages further render the so-called "adverse reaction" regarding seriously hazardous weight gain unclear and ambiguous because on the one hand, the label and company data revealed that 23%-33% or more of Seroquel users will experience clinically significant weight gain, but the sales message was that the drug is "weight neutral" causes "minimal weight gain" or has a "favorable weight profile." These sales messages not only contradicted what AstraZeneca knew about weight gain and Seroquel, from my review of Seroquel clinical trial data and company documents, they actually contradicted Seroquel's own approved label, undermining the clarity, accuracy, and unambiguousness of the label.

9. With respect to the pre-2004 label concerning hyperglycemia and diabetes mellitus, it is my opinion that AstraZeneca obscured and buried any mention of hyperglycemia and diabetes in the pre-2004 label by simply mentioning those words and characterizing the conditions as "infrequent" in the adverse reactions section of the label. AstraZeneca further obscures and confuses the issue by also listing "hypoglycemia" and "weight loss" as "infrequent" adverse reactions. This is simply no warning at all as to the true frequency and severity of those side effects suffered by Seroquel users. Documents I have reviewed showed that the company knew, prior to Seroquel's launch, that statistically significant weight gain increases by Seroquel users, would seriously impact patient health in terms of glucose dysregulation. Moreover, at least by 2000, documents I reviewed showed

that the company's medical safety director had concluded that Seroquel can cause impaired glucose dysregulation including diabetes.

10. The pre-2004 label is inadequate to warn prescribing physicians of the nature, severity, and frequency of the risk of hyperglycemia and diabetes mellitus associated with Seroquel, and for the above reasons is unclear, inaccurate, and ambiguous. It does not convey in a meaningful way the toxic potential of the drug and is confusing.

11. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined any attempt by AstraZeneca to warn of hyperglycemia and diabetes mellitus in the pre-2004 label. For example, Dr. Nasrallah's 2002 paper cites a now discredited study by Dr. Reinstein suggesting that Seroquel patients lost weight and had their diabetes cured after taking Seroquel for ten weeks.

12. With respect to the 2004-2007 label for Seroquel regarding hyperglycemia and diabetes mellitus, the so-called "class label" warning section on hyperglycemia and diabetes is inadequate, unclear, and ambiguous because it is laced with generalities, disclaimers, and distracting verbiage. Specifically, it fails to accurately and clearly state the measured increases in new onset diabetes that are specific to Seroquel, which were significantly greater based on clinical trials and company documents that I have reviewed as compared to certain other second generation antipsychotics that also bear the class label warning.

13. Moreover, the class label neglects to accurately describe the level of Seroquel's risk of those side effects, which was extraordinary according to the clinical trials

and company documents that I have reviewed and as compared to second generation antipsychotics such as aripiprazole and ziprasidone, which studies show do not cause clinically significant weight gain and hyperglycemia/diabetes. Instead, the 2004-2007 label describes merely that hyperglycemia and related serious complications "has been reported" without any data whatsoever quantifying the rate of incidents and severity of such risks and complications, or identifying which second generation antipsychotics were the subject of such "reports." The label language then further waters down the "warning" by indicating that measurement of glucose abnormalities is complicated by factors such as an increased rate in diabetes among the schizophrenic or general populations. This warning is far from a model of clarity and unambiguousness given the conclusions that the company and other foreign regulatory bodies reached that a reasonable association between Seroquel and hyperglycemia/diabetes (if not a causal association as well) had already been established before and during the time period this label was in effect.

14. In addition, AstraZeneca's marketing materials and sales representatives' direct message "discussions" to physicians during this time further undermined and diluted the warning. For example, company documents reveal that physicians were still receiving correspondence from the company referencing the Reinstein study concluding that Seroquel may cause weight loss and reverse diabetes in sizeable numbers of patients. Other internal company communication revealed that the Brecher article was still being disseminated. The FDA also reprimanded AstraZeneca in 2006 for failing to disclose in promotional material the increased risk of hyperglycemia and diabetes mellitus in patients treated with Seroquel, resulting in the promotional material being "misleading" and "undermin[ing] the warning."

15. Based on clinical experience, the so-called class label warning is inadequate to communicate the true nature and severity of the hyperglycemia/diabetes mellitus risk associated with Seroquel alone to physicians prescribing Seroquel to their patients.

16. Additionally, based on documents I have reviewed, language associated with the class label warning was a product of negotiations between AstraZeneca and the FDA. For example, with respect to the January 2004 "Dear Doctor" letter relative to the "class label" warning sent by AstraZeneca, earlier correspondence between the FDA and AstraZeneca revealed that AstraZeneca desired to characterize the new "warning" as simply being "about hyperglycemia and diabetes in patients taking these medications," but the FDA stated that it "preferred" the statement "describing increased risk of hyperglycemia and diabetes in patients taking these medications." From the correspondence I reviewed, it appears as though AstraZeneca determined not to further press the issue with the FDA.

17. With respect to the label change that occurred in 2007 regarding the hyperglycemia and diabetes mellitus warning contained on Seroquel, while it directs one to new language in the "adverse events" section, it is my opinion that the 2007 label change is still inadequate because it fails to clearly, accurately, and unambiguously describe the alarming rate at which Seroquel users in long-term clinical trials contracted diabetes, and the necessary warning language that a prescribing physician would expect to see relative to that very significant risk is not contained in the "warnings" section. Instead mere cross-reference is made to clinical trials data the "adverse reactions" section. The "adverse reactions" section does not mention the word "diabetes," but examination of the data reveals that Seroquel patients in long-term clinical trials were over twice as likely to suffer diabetes than

patients taking placebo. Company documents that I have reviewed show that AstraZeneca has characterized the risk of diabetes-level blood glucose abnormalities associated with Seroquel as "common." The label is facially unclear, inaccurate, and misleading because the frequency and severity of the diabetes risk is not mentioned in the "warnings" section but instead is buried in the "adverse reactions" section, and because what is truly diabetes-level blood sugar is characterized merely as "hyperglycemia" and "increased blood sugar"—i.e., fasting blood glucose measurements (those taken 8 hours after a meal) that are $\geq$ 126 mg/dL or non-fasting blood glucose measurements $\geq$ 200 mg/dL is frank diabetes, not merely hyperglycemia. The label is also inadequate because it fails to clearly and unambiguously warn of a "cause and effect" relationship between Seroquel use and diabetes-level blood glucose abnormalities.

18. The FDA is not satisfied with AstraZeneca's most recent Seroquel label change, as indicated in the June 2008 correspondence I have reviewed from the FDA to AstraZeneca. The FDA requested that the updated label be changed to add the additional information that "[t]he mean change in glucose from baseline was +5.0 mg/dl for SEROQUEL and –0.05 mg/dl for placebo," indicating that the FDA desires for AstraZeneca to reveal that there was more than a 5-fold increase in blood glucose levels between those subjects taking Seroquel and those taking placebo. The FDA also asked that AstraZeneca add the statement: "Because of limitations in the study design of these long-term trials as well as lack of confirmed fasting glucose data, the effects of Seroquel on blood glucose may be underestimated." In its letter, the FDA supported the additional statement above as follows:

> Since the 2-week long-term placebo-controlled bipolar maintenance trial studies were randomized withdrawal trials, there is some bias in that only subjects who were able to tolerate quetiapine in the open-label phase are then randomized. If subjects did not tolerate quetiapine in the open label phase, if they dropped out due to elevations in blood glucose for example, they would not be randomized and the overall effect of the drug on this parameter would be skewed. Therefore, because of this design issue, the overall effect of Seroquel on blood glucose could be underestimated.

Thus, the FDA wanted to provide clarity that the already negative blood glucose results stated in the new label—based on studies that effectively prescreened participants who did not well-tolerate Seroquel—actually may be even worse than the label reveals. AstraZeneca has not made the labeling changes that the FDA has requested as of the date of execution of this Declaration. AstraZeneca's evasive treatment and abstruseness with respect to this label change further confirms my opinion that AstraZeneca has not been forthright with physicians who prescribe Seroquel in the sense of "full disclosure" of pertinent, potentially life threatening (or certainly life-altering) healthcare information such that physicians may fully consider the risks and benefits and adequately advise and consult with their patients.

19. Overall, the inadequacy of Seroquel's labeling and accompanying misstatements of the risks associated with its use make it prohibitively difficult for a physician relying on such information to appreciate the true nature of Seroquel's risks and discuss those risks with his or her patients.

20. Furthermore, in my opinion, AstraZeneca's warnings for Seroquel appear to have been designed to obscure known risks associated with the drug, rather than to clearly, accurately, and unambiguously communicate risks to prescribing physicians in a frank,

explanatory manner such that they would have ready access to such critical information in treating their patients.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this the 19th day of November, 2008.

William C. Wirshing, M.D.

CURRICULUM VITAE

WILLIAM C. WIRSHING, M.D.

Address

Work: Exodus Recovery Acute Treatment Center
3828 Delmas Terrace
Culver City, CA 90232

Tel (310) 253-9494

Home: 6433 Topanga Canyon Blvd. #429
Woodland Hills, CA 91303

Tel (310) 413-4200
Home Fax (818) 595-1367

E-mail: WIRSHING@UCLA.EDU

Birthdate 11 June, 1956

Birthplace Palo Alto, CA

Education

1982 M.D. - UCLA

1978 B.S. Electrical Engineering & Computer Science, University of CA, Berkeley

Internship, Residency, & Fellowship

1986-88 Postdoctoral Research Fellowship in Schizophrenia Research, UCLA, Department of Psychology, Los Angeles, CA

1983-86 Resident in Psychiatry, UCLA Neuropsychiatric Institute, Los Angeles, CA

1982-83 Intern in Medicine, UCLA Center for the Health Sciences & Wadsworth VA Medical Center, Los Angeles, CA

Licensure

1983 California License No. G 50986, DEA No. FW0654447

Certification

1991 Added Qualification in Geriatric Psychiatry, American Board of Psychiatry and Neurology (#000479)

1988 Diplomat, American Board of Psychiatry and Neurology (#30125)

Academic Appointments/Positions

2008- Medical Director Real Recovery. Agoura Hills, CA

2007- Vice President in charge of continuing medical education and research Exodus Corp. Los Angeles, CA

1996-06 Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1993-06 Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1993-96 Associate Professor of Clinical Psychiatry, Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine

1987-06 Director, Brentwood Movement Disorders Laboratory, West Los Angeles VA Medical Center

1988-93 Co-Chief, Schizophrenia Treatment Unit, West Los Angeles VA Medical Center, Brentwood Division

1986-93 Adjunct Assistant Professor of Psychiatry, Department of Psychiatry & Biobehavioral Sciences, UCLA School of Medicine

1986-88 Postgraduate Research Scholar, Department of Psychology, UCLA

1986-88 Co-Chief, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center

1985-86 Chief Resident, Geropsychiatry Treatment Unit, West Los Angeles Veterans Administration Medical Center, Brentwood Division

Awards & Honors

2006 Nominated for Golden Apple Award for Clinical years by graduating class of 2006

2003 Award in Recognition of Dedication in Teaching Excellence from the Graduating Class of 2003, David Geffen School of Medicine at UCLA

1999 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1999 Lucien B. Guze Golden Apple Award for Outstanding Teaching Class of 2001, UCLA School of Medicine

1998 Certificate of Excellence, West Los Angeles Success 98 Award Program, West Los Angeles Veterans Administration Medical Center

1996 Distinguished Educator Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1994 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1993 UCLA Medical School. Class of 1995 - Outstanding Teacher Award

1991 Departmental Teaching Award, UCLA School of Medicine, Department of Psychiatry & Biobehavioral Sciences

1988 Travel scholarship to attend the 4th Biannual Workshop on Schizophrenia in Badgastein, Austria.

1982 Sandoz Award for Excellence in the Behavioral Sciences

1982 Alpha Omega Alpha

1978 Tau Beta Pi (Engineering National Honor Society)

1978 Phi Beta Kappa

1978 B.S. Summa Cum Laude

Major Teaching Experience

2007- Weekly Continuing Medical Education Lecture Exodus Urgent Care Center, Culver City, CA.

2000-06 Case Conference: Diagnostic Dilemmas - Psychiatry (#425 Sec. 5) This weekly case conference focuses on differential diagnosis, with an emphasis on the various etiologies of psychotic symptoms including schizophrenia, substance-induced psychosis, malingering,and other disorders.

1995-06 Movement Disorders Seminar - Psychiatry (#446) a weekly, clinical based, interactive seminar focusing on the examination and treatment of patients with a broad range of movement disorders for psychiatry residents,

	neurobehavior fellows, medical students, and research staff (with DA Wirshing, M.D., CS Saunders, M.D., and JM Pierre, M.D.). (1.5 hrs/week)
1992-2004	Course director - Psychopathology (#201) for 2nd-year medical students. (6 hrs/week)
1991-2002	Faculty sponsor - Student Research Program. (1-8 hrs/week)
1990-1992	Faculty advisor for biweekly seminar for psychiatry residents on critical reading of the literature (with Joel Yager, MD, and Alison Doupe, MD, PhD). (1 1/2 hrs/2 weeks)
1989-92	Movement Disorders Seminar (Psychiatry Course #453), a weekly forum for psychiatry residents, neurobehavior fellows, and medical students (with JL Cummings, MD). (1 hr/week)
1988-1991	Class Organizer/Lecturer of "Topics in Geropsychiatry", a weekly seminar for psychiatry residents, medical students, and psychology interns. (1 1/2 hrs/week)
1988-06	Ward teaching supervisor (Psychiatry Course #403) for 1st- and 3rd-year psychiatric residents and for 3rd- and 4th-year medical students on the Schizophrenia Treatment Unit, BVAMC. (9 hrs/week)
1986-06	Off-ward teaching supervisor (Psychiatry Course #403) for 1st-, 2nd-, and 3rd-year psychiatric residents in the UCLA Residency Training Program. (2-4 hrs/week)
1986	Lecturer: "The Psychiatric Hospital in Historical Perspective" (with Dora B Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.
1985-88	Ward teaching supervisor for first- and second-year psychiatric residents and for first-year geriatric medicine fellows on the Geropsychiatry Ward, WLA/VAMC.
1985	Lecturer: "The Historical Roots of Modern Medicine" (with Dora Weiner, PhD), a class for undergraduates, College of Letters and Sciences, UCLA.

Hospital/University Committees

2005-06	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
2000-02	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1999-03	Medical Student Education Strategic Planning Committee
1999-02	Human Subjects Protection Committee, Veterans Affairs
1998	Neuroscience Sub Committee, UCLA School of Medicine
1997- 00	Faculty Executive Committee
1997- 01	Voluntary Clinical Faculty Academic Appointments and Adjustments Committee

1996-99	Second Year Curricular Block Planning Committee, UCLA School of Medicine
1995-98	Academic Advancement Committee Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine
1992-94	Ad Hoc Committee for Dementia, UCLA School of Medicine
1992-96	Student Affairs Committee, UCLA School of Medicine
1992-94	Human Subjects Protection Committee, Veterans Affairs
1991-93	Residency Fellowship Nominating Committee, UCLA
1991	Chief of Psychiatry Search Committee, Veterans Affairs
1990-93	Residency Education Curriculum Committee, UCLA
1988-90	Human Subjects Protection Committee, Veterans Affairs
1988-03	Pharmacy and Therapeutics Committee, Veterans Affairs

Grants Awarded

2005-06 "Management of Antipsychotic Medication Associated Obesity"
Co-Principal Investigator Donna A. Wirshing, M.D. PI
VA Merit Review

2005-06 "Relapse Prevention: Long Acting Atypical Antipsychotics"
Co-Investigator , Donna A. Wirshing, M.D. PI
NIMH RO1 (Multicenter Collaborative)

2002-05 Veterans Affairs Merit Review
"Cigarette Smoking by Schizophrenic Patients (Phase II)"
Collaborator. Jarvik Murray, M.D., Ph.D. - P.I.

2000-02 National Institute of Mental Health, MH41573-11A1
"Management for Risk of Relapse in Schizophrenia"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

2000-03 National Institute of Mental Health, MH59750-01A1
"Treatment of Negative Symptoms and Cognitive Impairments"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1998-00 Veterans Affairs Merit Review
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-02 Veterans Affairs Merit Review
"Quetiapine vs. Haloperidol Decanoate for the Long-Term Treatment of Schizophrenia and Schizo-Affective Disorder"
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1995-98 National Institute of Health, 1R01-DA09570-01A1
"Dopaminergic Modulation of Nicotine Reinforcement"
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1995-99 National Institute of Health, 1R01-MH46484-01
"New Antipsychotics: Clinical Trials and Naturalistic Follow-up."
Co-Investigator. Stephen R Marder, MD - P.I.

1993-95 Veterans Affairs Merit Review to examine cigarette smoking by schizophrenic patients.
Co-Investigator. Murray E. Jarvik, MD, PhD - P.I.

1993-96 Veterans Affairs Merit Review to examine the risks and benefits of typical and atypical antipsychotic drugs in the treatment of acute psychotic episodes.
P.I.

1992-95 National Institute of Health: MH46484-03
"Clozapine - Treatment Response and Disability."
Co-Investigator.

1990-92 NARSAD (National Alliance for Research on Schizophrenia and Depression) Young Investigators Grant to develop a method of quantifying drug-induced akathisia and to apply this method of determining the relative akathisic liability of the atypical neuroleptic clozapine.

1986-05 National Institute of Health: MH41573
"Management of Risk of Relapse in Schizophrenia."
Co-Investigator. Stephen R Marder, MD and Robert P. Liberman, MD Co-P.I.s

1988-90 Veterans Affairs Merit Review to examine the feasibility of using a battery of electromechanical instruments to prospectively follow patients with tardive dyskinesia.
Co-Investigator. JL Cummings, MD, P.I.

1988-89 NARSAD Young Investigators Grant to continue research on the instrumentation of drug-induced movement disorders.

1987-88 Biomedical Research Support Grant from the Department of Psychiatry, UCLA School of Medicine, to develop a system to measure and analyze the movements of the human larynx.

Industry Sponsored

Investigator Designed and Initiated

1999-03 Janssen Pharmaceutica: Investigator designed protocol.
"Brief Hospitalization for Schizophrenia: Strategies to Improve Treatment Outcome"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

2000-05 Eli Lilly, Inc.: Investigator designed protocol.
"Olanzapine vs. Risperidone in Treatment Refractory Schizophrenia"
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

Industry Designed and Initiated

1998-99 Merck & Company, Inc.
"A Double-Blind, Active and Placebo-Controlled, Safety Tolerability, and Preliminary Antipsychotic Activity Study of MK-0869 in Hospitalized Schizophrenia Patients"
P.I. William C. Wirshing, M.D.

1998-99 Hoechst Marion Roussel, Inc.
"A Multicenter, Placebo and Active Control, Double-Blind Randomized Study of the Efficacy, Safety and Pharmacokinetics of M100907 (10 and 20 mg/d in Schizophrenic and Schizoaffective Patients."
Co-Investigator. Donna A Wirshing, M.D. - P.I

1997-00 Organon 041002
"A Double Blind, Five-Armed, Fixed Dose, Active and Placebo Controlled Dose-Finding Study With Sublingual ORG 5222 in Subjects With Acute Phase Schizophrenia"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 42,776
"An Open Label Follow-on Study on the Long-Term Safety of Aripiprazole in Patients with Psychosis"
P.I. William C. Wirshing, M.D.

1997-99 Otsuka America: 31-97-202
"A Phase III Double-Blind Study of Aripiprazole and Risperidone in the Treatment of Psychosis"
P.I. William C. Wirshing, M.D.

1997-98 Janssen Pharmaceutica: RIS-USA-112
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1997-99 Janssen Pharmaceutica: RIS-USA-113
"A Multicenter, Randomized, Double Blind, Parallel Group Trial Comparing the Safety and Efficacy of Risperidone and Olanzapine in the Treatment of Psychosis in Patients with Schizophrenia and Schizoaffective Disorder."
Co-Investigator. Donna A. Wirshing, M.D. - P.I.

1995-98 Hoechst Marion Roussel
"An Open-Label, Follow-Up, Multicenter, Long-Term Maintenance Study of MDL 100, 907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-98 Otsuka: 31-95-201
"OPC-14597: An Open-Label Tolerability Study in Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1995-96 Hoechst Marion Roussel: IND# 47,372
"A Randomized, Double-Blind, Placebo-Controlled, Parallel, Multiple Dose, Multicenter Study to Determine the Safety, Tolerability, Pharmacokinetics, and Biochemical Activity of MDL 100,907 in Patients with Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1995-96 Merck & Company, Inc.
"A Double-Blind, Placebo-Controlled, Safety, Tolerability and Preliminary Antipsychotic Activity Study of L-745,870 in Hospitalized Schizophrenic Patients"
P.I. William C. Wirshing, M.D.

1995-96 Otsuka: 31-94-202
"A Dose Ranging Study of the Efficacy and Tolerability of OPC-14597 in Acutely Relapsing Hospitalized Schizophrenic Patients."
P.I. William C. Wirshing, M.D.

1993-97 Eli Lilly Incorporated: F1D-MC-HGAP
"Fixed Dose Olanzapine versus Placebo in the Treatment of Schizophrenia."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-99 Pfizer, Inc.: 128-116B
"A 52-Week, Open Extension Study Evaluating the Safety and Outcome of 40-80 mg BID of Oral Ziprasidone (CP-88,059-1) Daily in the Treatment of Subjects Who Have Participated in Previous Ziprasidone Clinical Trials."
Co-Investigator. Donna Ames, M.D. - P.I.

1993-94 R.W. Johnson: M92-083
"Multi-Center, Randomized, Double-Blind, and Controlled, 4 Week, Multiple Oral Rising Dose Study to Determine Safety Tolerability, Pharmokinetics and Behavioral Activity of RWJ-37796 in Male Schizophrenic Subjects Phase II."
P.I. William C. Wirshing, M.D.

1992-98 Abbott Laboratories - Neuroscience Venture: M92-795
"An Open Label Assessment of the Long Term Safety of Sertindole in the Treatment of Schizophrenic Patients."
Co-Investigator. Donna Ames, M.D. - P.I.

1994-96 Pfizer, Inc.: 128-115
"Phase III, Six Week, Double Blind, Multi-Center, Placebo Controlled Study Evaluating the Efficacy and Safety of Three Fixed Doses of Oral Ziprasidone (CP-88,051-1) and Haloperidol in the Acute Exacerbation of Schizophrenia and Schizo-Affective Disorder."
Co-Investigator. Donna Ames, M.D. - P.I.

1992-94 Glaxo, Inc.: S3B-201
"A Randomized, Double-Blind, Placebo-Controlled, Crossover Evaluation of the Effects of GR68755C on Serum Levels of Haloperidol in Patients with a Diagnosis of Schizophrenia."
Co-Investigator. Stephen R. Marder, M.D. - P.I.

1992-93 Abbott Laboratories - Neuroscience Venture: M92-762
"A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Sertindole in Schizophrenic Patients."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1992-93 Schering Plough Research Corporation: SCH39166
"Safety, Tolerance and Pilot Efficacy of Rising Multiple Doses of SCH39166: An Open Label Trial."
Co-Investigator. Stephen R Marder, M.D. - P.I.

1988-89 Astra Pharmaceuticals
"Raclopride in Schizophrenia: a Haloperidol-Controlled, Double-Blind, Dose-Finding Clinical Trial."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

1990-91 Sandoz Pharmaceuticals
"A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Multi-Stage, Dose-Finding Study of SDZ HDC 912 in DSM-III-R Defined Hospitalized Schizophrenic Patients."
Co-Investigator. Theodore Van Putten, M.D. - P.I.

Reviewer / Editor

Reviewer:

American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Brain Dysfunction
CNS Spectrums
Comprehensive Psychiatry

International Journal of Psychiatry in Medicine
Journal of Clinical Psychiatry
Journal of Psychiatric Research
Journal of Clinical Psychopharmacology
Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Psychiatry Research
Psychopharmacology
Psychopharmacology Bulletin
Psychosomatics
Schizophrenia Bulletin

Invited Presentations

04/07 "Schizophrenia and Related Psychoses" Grand Rounds Northridge Hospital, Northridge CA 15 Apr 2007

08/06 "Tailored Management of Schizophrenia in the Real World: A Naturalistic Approach" Presented at Evansville State Hospital, Evansville, IN, 17 Aug 06

08/06 "The Metabolic Mayhem of Atypicals: The TD of the New Millennium" Grond Rounds Antelope Valley Hospital 11 Aug 06.

08/06 "Use of Atypical Antipsychotics in Bipolar Illness"1 Aug 06 Honolulu, HI.

03/06 "Treatment of Agitation with Behavioral Interventions and Atypical Antipsychotics in Schizophrenia" Presented at American Association for Geriatric Psychiatry, San Juan, Puerto Rico, 11 Mar 06.

02/06 "Addressing Metabolic Disturbances with Antipsychotic Treatments" Presented at San Francisco General Hospital, Dept of Psychiatry, San Francisco, CA, 24 Feb 06

12/05 "Metabolic Impact of Atypical Antipsychotics: The View from Two Decades of Experience" Presented at Eden Medical Center, Castro Valley, CA 7 Dec 2005

11/05 "Clinical Management of Behavioral and Psychological Symptoms in Dementia" Presented at Salem Hospital, Salem, OR, 16 Nov 05

10/05 "Marketing Atypical Antipsychotics and the Opacity of Adiposity" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 26 Oct 05

07/05 "Treatment of Agitation in Elderly Demented Patients" Presented at Grand Rounds, Hawaii State Hospital, Kaneohe, HI, 12 Jul 05

07/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 12 Jul 05

04/05 "Metabolic Disturbances During Antipsychotic Treatment" Presented at Grand Rounds, Battle Creek VA Med Center, Battle Creek, MI, 7 Apr 05

12/04 "Considerations in Long-Term Management of Schizophrenia" Presented at Grand Rounds, Corcoran State Prison, Corcoran, CA 1 Dec 04

12/04 "Management of Associated Comorbidities of Schizophrenia" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA 1 Dec 04

09/04 "Pharamacological Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Scripps Mercy Hospital, San Diego, CA, 7 Sep 04

08/04 "Metabolic Disorder" Presented at Grand Rounds, Kedren Hospital, Los Angeles, CA 16 Aug 04

06/04 "Atypical Antipsychotics in Special Populations" Presented at Grand Rounds Terrell State Hospital, Terrell, TX, 21 Jun 04

06/04 "The Many Faces of 'Wartime' PTSD" Presented at Grand Rounds, Mountain Crest Hospital, Fort Collins, CO, 15 Jun 04

05/04 "Pharmacology Treatment of Psychosis and Agitation in Dementia of the Elderly" Presented at Grand Rounds, Utah State Hospital, Provost, UT, 20 Mau 04

05/04 "Psychiatric Research Ethics" Presented at NIH Neuroscience Center, Bethesda, MD, 17 May 04

05/04 "Lab Science to Clinical Practice: Neurochemical Model of Antipsychotic Effects" Presented at Grand Rounds, Metropolitan State Hospital, Norwalk, CA, 12 May 04

04/04 "New Indications for Antipsychotics for Bi-Polar Disorders" Presented at Grand Rounds, Cedars Sinai, Los Angeles, CA, 29 Apr 04

03/04 "A Century after Bleuler, What Do We Really Know About Schizophrenia, Its Origin, Cause, and Treatment?" Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

03/04 "The Antipsychotics: Their Developmental History, Clinical Limitations, Major Toxicities, and Anticipated Future." Presented at WASP (World Association of Social Psychiatry), 1st Regional Congress of Social Psychiatry in Africa; Johannesburg, Gauteng, 24 Mar 04

02/04 "Consideration in the Long-term Management of Schizophrenia" Presented at Grand Rounds, Stanford University Hospital, Stanford, CA, 19 Feb 04

02/04 "The Marketing of Atypical Antipsychotic Drugs: A War for Our "Loyalties" Moves Into its Guerilla Phase" Presented at Grand Rounds, Sepulveda VA Mental Health Center, Los Angeles, CA, 11 Feb 04

02/04 "Drug Induced Metabolic Symptoms with Antipsychotic Paradigm Shift in an Approach to Patient Care" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 4 Feb 04

01/04 "Risperdal Consta" Presented at Grand Rounds, Indianapolis VA, Indianapolis, IN, 15 Jan 04

12/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Riverside County Department of Mental Health, Hemet CA, 9 Dec 03

12/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Castle Medical Center, Kailua, HI, 2 Dec 03

11/03 "Monitoring Patients on Antipsychotic Drugs for Glucose Intolerance and Other Features of the Metabolic Syndrome" Presented at Alexandria, VA, 19-20 Nov 03

11/03 "Antipsychotics: Overcoming Side Effect Treatment Barriers" Presented at Grand Rounds, Long Beach VA Medical Center, Long Beach, CA, 12 Nov 03

11/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, Fresno, CA, 11 Nov 03

11/03 "A Broad Spectrum in Psychotropics" Presented at Grand Rounds, Golden Valley Health Center-Corner of Hope, Modesto, CA, 6 Nov 03

10/03 "The Mechanistic Similarities and Distinctions Among Antipsychotics: A Treatment Refractory Model" Presented at Grand Rounds, Hawaii State Hospital Auditorium, Oahu, HI, 24 Oct 03

10/03 "The Side Effects of the Atypical Antipsychotics: Marketing Mischief, Metabolic Mayhem, or Mechanistic Magic?" Presented at Grand Rounds, San Francisco Clinic, San Francisco, CA, 4 Oct 03

10/03 "Kaiser/Group Health Cooperative AP Advisory Board" Presented at San Francisco, CA, 4 Oct 03

10/03 "Improvement in Cognitive Function, Dosing and Titration" Presented at Grand Rounds, Olive View Hospital, Sylmar, CA, 2 Oct 03

09/03 "Strategies for Controlling Psychotic Symptoms" Presented at Grand Rounds, Seattle Hospital, Seattle, WA, 11 Sep 03

08/03 "Neurocognition and Schizophrenia Including Issues on Nicotine Receptors" Presented at Grand Rounds, Ventura County Behavioral Health Inpatient Unit, Ventura, CA, 13 Aug 03

05/03 "Switchover from Clozapine to Quetiapine: Mixed Results" Presented at Biological Psychiatry, San Francisco, CA, 15 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, Eugene VA Clinic, Eugene, OR, 13 May 03

05/03 "Effects of Novel Antipsychotics on Glucose and Lipid Levels" Presented at Grand Rounds, VA Medical Center, Portland, OR, 12 May 03

05/03 "Atypical Antipsychotics: Marketing Mischief or Metabolic Mayhem" Presented at Grand Rounds, Harbor-UCLA Medical Center, Torrance, CA, 6 May 03

04/03 "Metabolic Consequences of Antipsychotic Therapy" Presented at Grand Rounds, Atascadero State Hospital, Atascadero, CA, 30 Apr 03

03/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, RJ Donovan Correctional Facility, San Diego, CA, 12 Mar 03

03/03 "Aripiprazole" Presented at Grand Rounds, Patton State Hospital, Patton, CA, 5 Mar 03

02/03 "Applied Neuropsychopharmacology: The Spectrum of Clinical Outcomes with Atypical Antipsychotics" Presented at the CNS Advisory Summit, Scottsdale AZ, 22 Feb 03

02/03 "The Use of Atypical Antipsychotics in Mood Disorders" Presented at Grand Rounds, Region IV Parole Headquarters, Diamond Bar, CA, 21 Feb 03

01/03 "Metabolic Side Effects of Atypical Antipsychotics" Presented at Grand Rounds, King Drew Medical Center, Los Angeles, CA, 28 Jan 03

01/03 "TD - What if Anything is New?" Presented at Grand Rounds, VA Hospital, Neurology Department, Los Angeles, CA, 24 Jan 03

01/03 "Metabolic Toxicities of Atypical Antipsychotic Agents: Speculations, Etiology, and Treatment" Presented at Grand Rounds, Sepulveda VA, Los Angeles, CA, 22 Jan 03

12-02 "Aripiprazole" Presented at Grand Rounds, Loma Linda University, Redlands, CA 20 Dec 02

12-02 "Aripiprazole" Presented at Grand Rounds, Arrowhead Regional Medical Center, Colton, CA, 17 Dec 02

12-02 "Treatment Emergent Movement Disorders in Current Clinical Practice" Presented at Grand Rounds, Queens Hospital, Honolulu, HI, 13 Dec 02

12-02 "Advancement in Treatment of Schizophrenia" Presented at Grand Rounds, Tripler VA Army Hospital, Honolulu, HI, 11 Dec 02

11-02 "Evolution of Antipsychotic Therapies: A Pathophysiologic Approach" Presented at National Network if Psychiatric Educators, Laguna Niguel, CA, 15 Nov 02.

10-02 "Side Effects Involving Newer Antipsychotic Medications Including Risk of Cardiovascular Disease and Diabetes" Presented at Grand Rounds, Bakersfield Memorial Hospital, Bakersfield CA, 24 Oct 02.

03-02 "The Atypical Antipsychotic Compounds: What is the Crucial Difference Among Them?" Presented at Psychopharmacology Course, Stanford University, Stanford CA, 9 Mar 02.

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Waco, TX, 7 Mar 02

03-02 "The Relative Metabolic Toxicities Among the Newer Antipsychotic Compounds." Presented at Grand Rounds, Dallas VA Medical Center, Dallas, TX, 7 Mar 02

11-01 "Aripiprazole: Is anything Really New in the Wold of Antipsychotic Medications?" Presented at Abilitat Investigators Meeting, Scottsdale, AZ, 29 Nov 01.

09-01 "The Past, Present, and (Near) Future of Antipsychotic Medications: The Under-appreciated Role of Luck!" Presented at The Annual Meeting of the Northern California Psychiatric Society, Saratoga, CA, 19 Sep 01.

07-01 "The Metabolic Side Effects of the Newer Antipsychotic Compounds: The TD of the New Millennium." Presented at Grand Rounds, UC Irvine, Irvine, CA, 17 Jul 01.

05-01 "The Toxicities of the So-Called 'Atypical Antipsychotics'--Focus on Dyslipidemia." Presented at Grand Rounds, Utah Neuropsychiatric Institute, Salt Lake City, Utah, 22 May 01.

04-01 "Prodromal Phase of Schizophrenia: Diagnosis and Treatment." Presented at W. Covina Mental Health Office, W. Covina, CA, 19 April 01.

03-01 "Risperidone: A Clinical Research Update." Presented at Le Royal Meridien, Toronto, Ontario, Canada, 31 Mar 01.

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Tennessee, Memphis, TN, 9 Feb 01

03-01 "Ziprasidone: A New Treatment Option for Schizophrenia." Presented at University Of Arkansas for Medical Science, Little Rock, AR, 8 Feb 01

02-01 "Use of Antipsychotic Drugs on Treatment Approach for Drug Induced Psychosis." Presented at San Quentin State Prison, San Quentin, CA, 21 Feb 01.

01-01 "EPA and TD with Novel Antipsychotics." Presented at Lanterman State Hospital, Pomona, CA, 25 Jan 01.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at VA Hospital, Seattle, WA, 15 Dec 00.

12-00 "Efficacy and Safety Data of the Atypical Antipsychotics." Presented at Atascadero State Hospital, Atascadero, CA, 14 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, VA Hospital Outpatient Clinic, Roseburg, OR, 12 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly" Presented at Grand Rounds, USC Ingleside Hospital, Rosemead, CA, 8 Dec 00.

12-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Grand Rounds, University of Southern California, Los Angeles, CA, 6 Dec 00.

11-00 "Safety and Efficacy Among Atypicals; Treatment Refractory Schizophrenia." Presented at Los Angeles County Jail, Los Angeles, CA, 30 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Olive View Hospital, Sylmar, CA, 16 Nov 00.

11-00 "Long-Term Outcomes with Antipsychotic Medications: The limitations of Our Current Technology." Presented at Ziprasidone National Consultants Forum, Scottsdale, AZ, 14 Nov 00.

11-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at USC Ingleside Hospital, Rosemead, CA, 9 Nov 00.

10-00 "Newer Antipsychotics: Approaches to Treatment Refractory Patients." Presented at 2000 MIRECC Retreat, Los Angeles, CA, 25 Oct 00.

10-00 "Weight Gain and Atypical Antipsychotic Medications: The TD of the New Millennium?" Presented at MHC of Greater Manchester, Manchester, NH, 12 Oct 00.

09-00 "Side Effects of Typical and Atypical Antipsychotic Agents." Presented at the UCLA Medical Plaza, Los Angeles, CA, 11 Sep 00.

09-00 "Safety and Efficacy Among Atypicals." Presented at Sacred Heart Hospital, Spokane, WA, 12 Sep 00

09-00 "Safety and Efficacy Among Atypicals." Presented at Skagit Valley Mental Health, Mt. Vernon, WA, 13 Sep 00.

09-00 "Update on Atypical Antipsychotics." Presented at Porterville Developmental Center, Porterville, CA, 14 Sep 00.

07-00 "Schizophrenia: Treatment with Risperdal." Presented at the Office of Mental Health, New Orleans, LA, 25 Jul 00.

07-00 "Atypicals and Treatment Resistant Schizophrenia." Presented at Loma Linda Behavior Medicine Center, Redlands, CA, 21 Jul 00.

06-00 "Movement Disorders." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 16 Jun 00.

06-00 "Tools for Assessing Symptoms: Side Effect Scales." Presented at Palacio de Exposiciones y Congresos, Seville, Spain, 17 Jun 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at UC Irvine Medical Neuropsychology Center, Orange, CA, 30 May 00.

05-00 "Optimal Management of Psychosis and Agitation in the Elderly." Presented at Dave & Buster's, Orange, CA, 24 May 00.

05-00 "The Side Effects of Antipsychotic Compounds." Presented at Kaiser Permanente, Fontana, CA, 17 May 00.

04-00 "Atypical Antipsychotics" Presented at Riverside County Inpatient, Riverside, CA, 27 Apr 00.

03-00 "The Novel Antipsychotics." Presented at Loma Linda University, Loma Linda, CA, 29 Mar 00.

03-00 "The Cardiovascular Liabilities of the Atypical Antipsychotics: The Next 'Big' Thing." Presented at Grand Rounds, University of Hawaii, 24 Mar 00.

03-00 "The New Antipsychotic Compounds Really 'New'?" Presented at Grand Rounds, Contra Costa County Regional Medical Center, Martinez, CA, 14 Mar 00.

03-00 "Treatment Refractory Schizophrenia: Is there a rational approach?" Presented at American Psychiatric Association & Nevada Association of Psychiatric Physicians, Las Vegas, NV, Sat, 4 Mar 00.

02-00 "The Use of Risperidone in Acutely Psychotic Patients." Presented at Italian Society of Psychopathology (V SOPSI Congress), Rome, Italy, 23 Feb 00.

02-00 "The Differential Toxicities Among the Atypical Antipsychotics." Presented at Grand Rounds, Cedars Sinai Medical Center, Los Angeles, CA, 17 Feb 00.

12-99 Visiting Scholar-numerous presentations, Presented at University of Arkansas, Little Rock, AR, 5-8 Dec 99

11-99 "The Novel Antipsychotic Medications." Presented at Anaheim, CA, 12 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at University of Kansas Medical Center, Kansas City, MO, 5 Nov 99.

11-99 "Atypicals Antipsychotics: Efficacy and Side Effects." Presented at The American Restaurant, Kansas City, MO, 4 Nov 99.

11-99 "Side Effects of Antipsychiatric Compounds." Presented at Colmery O'Neil V A M C, Topeka, KS, 4 Nov 99.

11-99 "The Side Effects of Antipsychotic Compounds." Presented at Western Missouri Mental Health South Auditorium, Kansas City, MO, 4 Nov 99.

10-99 "Is Clozaril still relevant?" Presented at Atascadero State Hospital, San Luis Obispo, CA, 14 Oct 99.

10-99 "Interested in Geriatric population & Economics of the drugs." Presented at Grand Rounds, Loma Linda University, Loma Linda, CA, 8 Oct 99.

09-99 "Side Effects of Atypical Antipsychotics: What can we expect in the short and long term?" Presented at Riverside, CA, 30 Sep 99.

09-99 "New Treatment Options in the Acute Management of Psychosis." Presented at New York, NY, 26 Sep 99.

08-99 "How to Choose the Correct Medication Regimen for the Treatment of Psychotic Manifestations." Presented at Lanterman Developmental Center, Pomona, CA, 26 Aug 99.

07-99 "Schizophrenia and Overview Movement Disorders." Presented at UCLA School of Nursing, Westwood, CA, 26 Jul 99.

07-99 "New and Novel Antipsychotics." Presented at Fairview Developmental Center, Costa Mesa, CA, 15 July 99.

06-99 "Schizophrenia-Current and New Treatment Trends." Presented at San Joaquin County Mental Health Services, Sacramento, CA, 24 Jun 99.

05-99 "Research Experience with the Newer Neuroleptics-Grand Rounds." Presented at Kaiser, San Francisco, CA, 25 May 99.

05-99 "New Treatment Options in the Acute Management of Psychosis." Presented at Boston Marriott Long Wharf, Boston, MA, 22 May 99.

05-99 "The Neurophysiology of Schizophrenia: Focus on the action of the Novel Antipsychotics." Presented at Kaiser, Woodland Hills, CA, 12 May 99.

04-99 "The New Generation of Antipsychotic Medications." Presented at Kaiser Sunset Family Practice, Los Angeles, CA, 26 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Leeds, England, United Kingdom, 9 Apr 99.

04-99 "Relative Efficacies and Toxicities of Risperidone and Olanzapine." Presented at Southampton, England, United Kingdom, 8 Apr 99.

04-99 "The Neurophysiology of Schizophrenia: Focus on the Action of the Novel Antipsychotics." Presented at The Schizophrenic Patient: Profiles, Diagnosis and Treatment Conference, Loma Linda University, Loma Linda, CA, 7 Apr 99.

03-99 "Pharmacological Bases for the Putative Neurocognitive Enhancing Impact of Atypical Antipsychotic Agents." Presented at Neurocognitive Impairment in Schizophrenic and Alzheimer's Disorders: Therapeutic Approaches Workshop, International Academy for Biomedical and Drug Research, Paris, FR, 12-13 Mar 99.

02-99 "Antipsychotic Toxicity in the Elderly." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Typical and Atypical Neuroleptics: A Geropsychiatric Perspective." Presented at 9th Annual Geriatric Psychiatry Conference, Dallas, TX, 13 Feb 99.

02-99 "Somatic Treatments of Psychotic Disorders" Given with course entitled "Recovery from Madness", Alex Kopelowicz, MD and Robert Liberman, MD--Course Chairs.

02-99 "The Comparative Toxicities of the New Antipsychotic Medications." Presented at Harbor UCLA, Torrance, CA, 2 Feb 99.

01-99 "The Treatment of Schizophrenia at the Turn of the Millennium: What Have We Learned?" Presented to local lay chapter of the California Alliance for the Mentally Ill, UCLA Medical Plaza, Los Angeles, CA, 14 Jan 99.

01-99 "Treatment Refractory Schizophrenia: The Role of the "New" Antipsychotic Compounds" Presented at Grand Rounds, UCI Medical Center, Irvine, CA, 5 Jan 99.

11-98 "Treatment of Schizophrenia." Presented at Grand Rounds, UC Davis Medical Center, Sacramento, CA, 11 Nov 98.

11-98 "Atypicals and Side Effects." Presented at Sutter Family Practice Residency Program, Sacramento, CA, 11 Nov 98.

11-98 "Treatment of Refractory Patients and Partial Response." Presented at Janssen-Cilag SpA Laboratories, Beerse, Belgium, 6 Nov 98.

10-98 "The Role of Novel Antipsychotics in the Control of the Acute Psychotic Symptoms." Presented at the WPA Symposium, Guadalajara, MX, 30 Oct 98.

10-98 "Efficacy of Risperdal and the Atypical Antipsychotics." Presented at Grand Rounds, Porterville State Hospital, Porterville, CA, 21 Oct 98.

10-98 "Treatment of the Refractory Patient." Presented at the Grand Geneva Resort Symposium, Lake Geneva, IL, 3 Oct 98.

10-98 "Treatment Resistant Schizophrenia" Presented at the APA-IPS Symposium, Los Angeles, CA, 2 Oct 98.

09-98 "Treatment Refractory Schizophrenia." Presented at Grand Rounds, Oregon Health Sciences University Department of Psychiatry, 29 Sep 98.

09-98 "The Second Generation of 'Anti-schizophrenic' Drugs." Presented at the 1998 William Rondeau Memorial Lecture, Oregon Health Sciences University Department of Psychiatry, 28 Sep 98.

09-98 "Movement Disorders in Psychiatry." Presented at VA Hines, IL, 23 Sep 98.

09-98 "The Role of Atypical Antipsychotics." Presented at Napa State Hospital, CA, 19 Sep 98.

09-98 "Atypical Antipsychotics and Schizophrenia." Presented at Grand Rounds, Menlo Park VAMC, Menlo Park, CA, 11 Sep 98.

08-98 "New Treatment Options in Schizophrenia." Presented at ComCare, Phoenix, AZ, 18 Aug 98.

07-98 "Schizophrenia Overview and Movement Disorders." Presented at the Neuropsychiatric Nurse Practitioner Program, UCLA School of Nursing, Los Angeles, CA, 27 Jul 98.

07-98 "New Treatment Interventions for Psychotic Disorders." Presented at San Joaquin County Mental Health Services, Stockton, CA, 16 Jul 98.

07-98 "Strategies for Rapidly Controlling Acute Psychotic Symptoms." Presented at Napa State Hospital, Napa, CA, 3 Jul 98.

06-98 "New Directions in Psychosis." Presented at Grand Rounds, San Francisco General Hospital, San Francisco, CA, 26 Jun 98.

06-98 "The Clinical Choice: Is an Algorithm Possible?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Treatment of Refractory Psychosis: Is There a Rational Approach?" Presented at Riverview Hospital, Vancouver, BC, 12 Jun 98.

06-98 "Drug Treatment of Schizophrenia" Presented as course number 63 with faculty S Marder, J Davis, P Janicak, at the 151st APA Annual Meeting in Toronto, Canada, 2 Jun 98.

05-98 "New Atypical Antipsychotics: Similarities and Differences" Presented via satellite program for Indio and Riverside County Mental Health Inpatient Treatment Facility, Riverside, CA, 28 May 98.

05-98 "New Advances in the Treatment of Schizophrenia" Presented by CME, Inc. at Sheraton Gateway, Los Angeles, CA, 17 May 98.

05-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs" Presented at Merritheu Memorial Hospital, Martinez, CA, 12 May 98.

05-98 "Management of Cognitive Disruption in Schizophrenia" Presented at University of Illinois at Chicago Symposium in Bloomingdale, IL, 5 May 98.

05-98 "Neurocognition, Schizophrenia, and the Role of the Novel Antipsychotic Medications" Presented at the Panhellenic Psychiatric Congress, Limnos, Greece, 2 May 98.

04-98 "Neurocognitive and Functional Assessment - Rationale for M100907 Superiority" Presented at second Neuropsychiatry Forum of Hoechst Marion Roussel in Bridgewater, NJ, 24 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Bergen Pines County Hospital, Paramus, NJ, 23 Apr 98.

04-98 "Treatment Resistant Schizophrenia: Is there a Rational Approach?" Presented at Rockland Psychiatric Center, Orangeburg, NY, 22 Apr 98.

04-98 "Update on Anti-psychotic Medications." Presented at Alaska Psychiatric Association's 5th Annual Spring Education Meeting, Anchorage, AK, 18 Apr 98.

03-98 "Psychopharmacology Update: A Comparison of Current Antipsychotic Drugs." Presented at Washington State Psychiatric Association Spring Meeting in Vancouver, BC, 28 Mar 98.

03-98 "Schizophrenia and Cognitive Function - Approaching the New Millennium" Presented at National Schizophrenia Symposium, Scottsdale, AZ, 27 Mar 98.

03-98 "Challenge: Making the most of Therapy with Atypical Antipsychotics" Presented at Eastern State Mental Hospital, Williamsburg, VA, 20 Mar 98.

03-98 "Past, Present and Future of Antipsychotic Drugs" Presented for the Virginia State Psychiatric Society, Richmond, VA, 21 Mar 98.

03-98 "Pharmacologic Impact on Neurocognitive Deficits in Schizophrenia:" Presented at Grand Round, Long Beach VA Medical Center, 4 Mar 98.

02-98 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates and Pharmacologic Responsivity" Presented at USC School of Medicine Grand Rounds, 10 Feb 98.

02-98 "Biological bases for Schizophrenia" Presented at the seminar course for undergraduates Psychiatry 98P Professional Schools Seminar Program, UCLA, CA, 4 Feb 98.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at V.A.Psychiatry Service Grand Rounds, Minneapolis, MI, 21 Nov 97.

11-97 "The New Generation of Antipsychotic Medications: Similarities and Differences" - Presented at HCMC Psychiatry Grand Rounds, MI. 21 Nov 97.

11-97 "Neurocognition in Schizophrenia: Magnitude, Functional Correlates, and Pharmacologic Responsivity" Presented at the Atascadero State Hospital, Atascadero, CA, 19 Nov 97.

11-97 "Pharmacologic Approach to Chronic and Treatment Refractory Schizophrenia" Presented at the Vancouver BCPA Conference, in Vancouver, Canada, 15 Nov 97.

11-97 "New Serotonin/Dopamine Antagonist" - Presented for the Loma Linda Psychiatric Residency Program, Loma Linda, CA, 14 Nov 97

11-97 "The Role of New Generation Antipsychotics in Treatment-Resistant Schizophrenia" - Presented in Grand Rounds at The Chicago Medical School Department of Psychiatry and Behavioral Sciences, Chicago, IL, 6 Nov 97.

10-97 "Beyond Conventional Symptoms" - Presented in Riyadh, Saudi Arabia, 20 Oct 97.

10-97 "Neurocognitive Changes in Schizophrenia" Clinical Pertinence and Impact of Pharmacotherapy" - Presented in Grand Rounds at the University of Nebraska Medical Center, Omaha, NE, 15 Oct 97.

09-97 "Treatment Resistance in Psychosis"- Presented at the Annual Meeting of the Huron Valley Medical Center in in Ypsilanti, MI, 24 Sep 97.

09-97 "Toxic Side Effects of Antipsychotic Medications - Focus on Neuromotor Syndromes" Presented at The Fall 1997 Symposium of Charter Behavioral Health Systems of New England, Nashua, New Hampshire, 20 Sep 97.

09-97 "Risperidone: Efficacy Beyond Conventional Symptoms" Presented at the 10th Annual Meeting of European College of Neuropsychopharmacology, Vienna, Austria, 15 Sep 97.

09-97 "Schizophrenia, Neurocognition, and Antipsychotic Meds" Presented in Grand Rounds at Oregon Health Science University, 9 Sep 97.

09-97 "Past, Present and Future of Antipsychotics" Presented at the Mendota Mental Health Institute Conference Center, Madison, WI, 29 Aug 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Midlands, England, 19 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in East Kilbride, England, 18 Jun 97.

06-97 "Efficacy: A Clinician's Evidence from Experience" Presented at the Risperdal: Evidence from Experience Interactive Seminars in Aberdeen, Scotland, 17 Jun 97.

06-97 "Antipsychotics: The Evidence from Experience" Presented at the Janssen Research Foundation in Beerse, Belgium, 16 Jun 97.

06-97 "Atypical Neuroleptics: Newer Antipsychotics" Presented at the Northampton VA Medical Center, Northampton, MA, 4 Jun 97.

05-97 "Beyond Conventional Symptoms: Focus on Risperidone" Presented in Grand Rounds at Vanderbilt University Medical Center, Nashville, TN, 27 May 97.

05-97 "Psychopharmacology in the Geriatric Patient: Utility and Limitations" Presented at the California Society of Internal Medicine annual meeting, San Diego, CA, 24 May 97.

05-97 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 54 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 150th APA Annual Meeting, San Diego, CA, 17-22 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Psychiatric Institute, Washington, DC, 16 May 97.

05-97 "Overview of Treatment of Psychosis with New Atypical Antipsychotic Medications" Presented at the Commission on Mental Health, Washington, DC, 15 May 97.

05-97 "Practical Applications in Atypical Antipsychotics: Clients with Movement Disorders" Presented at Cambridge Hospital, Boston, MA, 14 May 97.

05-97 "The Newer Antipsychotics: Differences and Applications" Presented at Butler Hospital, Providence, RI, 13 May 97.

04-97 "Risperidone and Neurocognition". Presented at the Annual Meeting of the Dutch Psychiatric Society, Amsterdam, Netherlands, 18 Apr 97.

04-97 "Clozapine vs. Haloperidol: Drug Intolerance in a Controlled Six Month Trial" Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

04-97 "Antipsychotic Drug Side-Effects: Objective and Subjective". Presented at the International Congress on Schizophrenia Research, Colorado Springs, CO, 14 Apr 97.

03-97 "An Update on Atypcial Antipsychotics". Presented in Hyannis, MA, 28 Mar 97.

03-97 "An Update on Atypical Antipsychotics". Presented in New Bedford, MA, 27 Mar 97.

03-97 "The Management of Acute Exacerbations in Chronic Schizophrenia". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "Beyond the Conventional Symptoms". Presented at Evidence From Experience, Lisbon, Portugal, 21 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Beijing, China, 17 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Nanjing, China, 15 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Shanghai, China, 14 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Wuhan, China, 12 Mar 97.

03-97 "The Efficacy of Risperidone: The Evidence from the Controlled Clinical Experience". Presented in Guangzhou, China, 11 Mar 97.

01-97 "Rational Approach to Antipsychotic Medications and Patient Selection". Presented at the Midwinter Program for Psychiatrists, Lake Tahoe, NV, 28 Jan 97.

01-97 "Current Therapy Options: Efficacy and Side Effects". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

01-97 "Issues in Diagnosis of Schizophrenia". Presented at the Reintegration: Therapeutic Horizons for Psychotic Disorders Symposium in Salt Lake City, UT, 25 Jan 97.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented to the Hawaii Psychiatric Medical Association, Waikiki, HI, 3 Dec 96.

12-96 "The New Generation of Antipsychotic Medications: Similarities & Differences". Presented at Hawaii State Hospital, Kaneohe, HI, 2 Dec 96.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Newcastle, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Glasgow, Scotland.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Birmingham, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented in Manchester, England.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Kyoto Prefectural University, Kyoto, Japan.

11-96 "Risperidone: The Controlled Clinical Experience". Presented at Hiroshima University, Hiroshima, Japan.

11-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented in Kurashiki (Okayama City), Japan.

08-96 "New Solutions to Treatment Resistant Schizophrenia". Presented at the 10th World Congress of Psychiatry, Madrid, Spain, 23 Aug 96.

07-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, Costa Mesa, CA.

06-96 "Critical Issues in Psychoses: Dementia, First-Break Patients, Refractory Cases, and Pharmacoeconomics of Schizophrenia". A CME presentation, San Francisco, CA.

06-96 "The New Generation of Antipsychotic Medications: How Are They Different?". A CME presentation, Staunton, VA.

05-96 "Treatment Resistant Schizophrenia" an industry-sponsored symposium presented at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

05-96 "The Recognition and Management of Side Effects of Typical and Atypical Neuroleptics" Presented as course number 61 with faculty SR Marder, J Davis, G Simpson, P Janicak at the 149th APA Annual Meeting, New York, NY, May 4-9, 1996.

03-96 "Treatment Resistant Schizophrenia: Is There a Rational Approach?" Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "The Natural History of the 'Schizophrenias'". Presented at Evolving Attitudes Across the Spectrum of Schizophrenia, Amsterdam, Netherlands.

03-96 "Update on New Antipsychotic Medications". Presented at University of California, Davis, Davis, CA.

03-96 "Special Populations with Psychoses: First Break Patients, Adolescents and Geriatric Patients". A CME presentation, Long Beach, CA.

02-96 "Psychopharmacology in the Elderly: Cognition and Psychosis". Presented at the Area 7 Symposium, Las Vegas, NV.

02-96 "Side Effects of Antipsychotics: Recognition and Treatment". Presented at Grand Rounds, Stanford University Medical Center, Palo Alto, CA.

01-96 "The History and Current Status of Antipsychotic Drug Development". Presented at Grand Rounds, The Palos Verdes Regional Psychiatric Hospital, Tucson, AZ.

01-96 "The Risk Benefit Profiles of the Serotonin-Dopamine Antagonists". Presented at the University of Arizona, Tucson, AZ.

12-95 "Rational Approaches to Antipsychotic Pharmacotherapy". Presented at the Quarterly Meeting of the County of San Diego Mental Health Services, San Diego, CA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, Seattle, WA.

11-95 "Special Populations with Psychosis: Adolescents, Geriatrics, and First Break Patients". A CME presentation, San Francisco, CA.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hirosaki University Department of Neuropsychiatry, Hirosaki University, Hirosaki, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Akita University School of Medicine Department of Psychiatry, Akita University, Akita, Japan.

10-95 "The New Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Hokkaido University Department of Psychiatry, Hokkaido University, Hokkaido, Japan.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the SinYang Park Hotel, KwangJu, Korea.

10-95 "Polypharmacy in the Treatment of Psychosis: Is There a Rational Approach?" presented at the KwangJu Severance Mental Hospital, KwangJu, Korea.

10-95 "Updáte on Serotonin/Dopamine Antagonists: Are They Really Different?" presented to the Meeting of the Korean Neuropsychiatric Association at the Seoul Education Culture Center, Seoul, Korea.

09-95 "Pharmacologic Treatment of Depression" presented to the Quarterly Meeting of the Hawaii Psychiatric Association, Honolulu, Hawaii.

09-95 "Anti-psychotic Medications & Patient Selection: Is There a Rational Approach?" presented to the Hawaii Medical Association at the University of Hawaii, Honolulu, Hawaii.

08-95 "Side Effects of Antipsychotic Medications" presented at the Quarterly Meeting of the Memphis Psychiatric Association, Memphis, TN.

07-95 "Polypharmacy: When is it Reasonable?" Grand Rounds, Alameda County Psychiatric Hospital, Alameda, CA.

07-95 "Behavioral Skill Training in Schizophrenia: Utility and Limitation" Grand Rounds, Atascadero State Hospital, Atascadero, CA.

06-95 "Side Effects of Antipsychotic Medications" Grand Rounds, Loma Linda VA Hospital, Loma Linda, CA.

06-95 "The Treatment of Psychosis in the Elderly" Los Encinas Hospital Annual Symposium, Pasadena, CA.

06-95 "Update on the New Antipsychotic Medications" presented to the Annual Meeting of the California Department of Corrections Psychiatrists, Diamond Bar, CA.

05-95 "How to do research without an NIMH grant" presented at the 148th Annual Meeting of the American Psychiatric Association, Miami, FL, 20-25 May 95.

05-95 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 69 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 148th APA Annual Meeting, Miami, FL, 20-25 May 95.

05-95 "Behavioral Skills Training in Chronic Schizophrenia" presented at the Annual Conference of Western Reserve Psychiatric Hospital, Northfield, OH, 5 May 95.

03-95 "Dopaminergic Modulation of Cigarette Smoking" presented at the Society for Research on Nicotine and Tobacco with Murray E Jarvik, MD, PhD and Nicholas H Caskey, PhD, San Diego, CA.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, St. Louis, MO.

03-95 "The Safety and Efficacy of Serotonin-Dopamine Antagonists" a Continuing Medical Education presentation, Philadelphia, PA.

02-95 "The Next Generation of Antipsychotic Medications" presented at Grand Rounds, Veterans Affairs Hospital, Tuskegee, AL.

11-94 "Dosing Strategies with Antipsychotic Compounds: Conventional, SDAs, and Atypicals" presented at the Fall Symposium of New Approaches to Treating Schizophrenia, Chicago, IL, 12 Nov 94.

10-94 "Risperidone: Is It Really Different?" presented at the Fall Conference of the California Alliance For the Mentally Ill, San Francisco, CA, 29 Oct 94.

05-94 "The recognition and management of the side effects of typical and atypical neuroleptics" presented as Course 71 with Director SR Marder, and Faculty J Davis, G Simpson, Philip Janicek, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 24 May 94.

05-94 "Dementia and Movement Disorders in the Elderly," presented as Course 6 with Director JL Cummings, and Faculty WE Reichman, D Sultzer, and myself, at the 147th APA Annual Meeting, Philadelphia, PA, 20 May 94.

04-94 "Risperidone, is it really different?" presented at a Stanford University sponsored symposium on the treatment of schizophrenia Palo Alto, CA.

03-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Utah State Alliance for the Mentally Ill, Salt Lake City, Utah.

02-94 "The New Atypical Antipsychotics--Focus on Risperidone" presented to the Washington State mental health workers (psychiatrists and pharmacists), Seattle, WA.

01-94 "The Real Cost of Neuroleptic Treatments" presented to the California State Legislature, Sacramento, CA.

01-94 "The Rational Use of Neuroleptics" presented at the annual educational meeting of the Los Angeles Chapter of Family Practioners, Santa Monica, CA.

10-93 "The Therapeutic Window--The Role of Subjective Experiences" presented at the Quarterly Meeting of the Royal College of Psychiatrists in London, England.

05-93 "Optimum Dosing in Maintenance Treatment." Marder SR, Van Putten T, Wirshing WC, Lebell MB, McKenzie J, Johnston-Cronk K, presented at the 146th APA Annual

Meeting, San Francisco, CA, 26 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 238. (No. 87B)

05-93 "Combined Skills Training and Early Intervention." Marder SR, Wirshing WC, Van Putten T, Eckman TA, Liberman RP, presented at the 146th APA Annual Meeting, San Francisco, CA, 24 May 93. In: 1993 CME Syllabus & Proceedings Summary, p. 156. (No. 28D)

05-93 "Clinical Use of Neuroleptic Plasma Levels." presented at the 146th APA Annual Meeting, San Francisco, CA, 25 May 93.

05-93 "Dementia and Movement Disorders in the Elderly," presented as Course 2 with Director JL Cummings, and Faculty WE Reichman and myself, at the 146th APA Annual Meeting, San Francisco, CA, 22 May 93.

01-93 "Hyperkinetic Syndromes in the Elderly" presented at the Geriatric Supercourse in Marina del Rey, CA, 20 Jan 93.

11-92 "Clinical Consequences of Akinesia and Akathisia", presented as first author with T Van Putten and SR Marder at the Association of European Psychiatrists Congress, Barcelona, Spain, 5 Nov 92.

10-92 "The New Atypical Antipsychotics", presented to the South Coast Chapter of the Alliance for the Mentally Ill, Torrance, CA.

06-92 "Impact of Public Opinion and News Media on Psychopharmacology in the 1990's", with Louis Jolyon West, MD, at the College of International Neuropsycho-pharmacology Annual Meeting (CINP), 30 Jun 92, Nice, France.

05-92 "Drug-Induced Movement Disorders in the Elderly," presented at the 145th Annual American Psychiatric Association Meeting, Washington, DC.

03-92 "Fluoxetine-Induced Suicidality: Science, Spurious, or Scientology?" presented at the Daniel X. Freedman Journal Club, UCLA.

01-92 "The Placebo-Controlled Treatment of the Schizophrenic Prodrome," Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

01-92 "Management of the Neuroleptic-Intolerant Patient," presented with D Ames and T Van Putten at UCLA Grand Rounds, Los Angeles, CA.

01-92 "Akathisia with the New Atypical Neuroleptics," presented at Psychiatry Grand Rounds, UCLA-Harbor Medical Center, Torrance, CA.

12-91 "Management of Risk of Rèlapse in Schizophrenia," presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico.

10-91 "Extrapyramidal Symptoms and the Atypical Antipsychotics," presented to the Southern . California Chapter of the California Alliance for the Mentally Ill, Los Angeles.

06-91 "Neuroleptic-Induced Extrapyramidal Symptoms," presented at the Southern California Psychiatric Society, West Hollywood, CA.

05-91 "Pharmacokinetics of Long-Acting Neuroleptics," presented with SR Marder, T Van Putten, J Hubbard, M Aravagiri, and KK Midha, at the American Psychiatric Association 144th Annual Meeting, New Orleans, LA.

05-91 "Fluphenazine Dose in Chronic Schizophrenia," presented with SR Marder, T Van Putten, M Lebell, J McKenzie, and K Johnston-Cronk, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

05-91 "Early Prediction of Schizophrenic Relapse," presented with SR Marder, T Van Putten, M Lebell, K Johnston-Cronk, and J Mintz, at the American Psychiatric Association Annual Meeting, New Orleans, LA.

04-91 "Instrumental Quantification of Akathisia," presented with T Van Putten, SR Marder, JL Cummings, G Bartzokis, and MA Lee at the International Congress on Schizophrenia Research, Tucson, AZ.

04-91 "Antipsychotic Drugs of the Future: The Legacy of Clozapine," presented at the Annual Meeting of the Southcoast Alliance for the Mentally Ill, Fountain Valley, CA.

02-91 "Free Radicals, Movements Disorders, and their Possible Interrelationship," presented to the College of Pharmacy, University of Saskatchewan, Saskatoon, Canada.

11-90 "Primary and Secondary Effects of the Neuroleptics: An Historical Perspective." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

11-90 "Antipsychotic Drugs of the Future: The Legacy of Clozapine." California Alliance for the Mentally Ill, Fall Conference, Ventura, CA.

10-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." 2nd Annual NARSAD Scientific Symposium, Washington, DC.

06-90 "Instrumental Quantification of the Akathisic Liability of Clozapine." Regional Meeting of NARSAD Supporters, Pasadena, CA.

02-90 "Instrumentation of Drug-Induced Movement Disorders." Neurology Grand Rounds, West LA VAMC, Los Angeles, CA.

02-90 "Functional Versus Organic Psychoses." Psychiatry Grand Rounds, UCLA Harbor Medical Center, Torrance.

10-89 "Use of Quantitative Instruments in the Assessment of Neuroleptic-Induced Movement Disorders." Presented to regional representatives of NARSAD.

04-89 "Management of Risk of Relapse in Schizophrenia. "The Annual Spring Scientific Meeting of the Southern California Psychiatric Society, Hollywood, CA.

03-89 "Quantitative Approaches to Drug-Induced Movement Syndromes." Medical Staff of Camarillo State Medical Facility, Camarillo, CA.

01-89 "Social Skills Training in the Chronic Schizophrenic: A Workshop." 2nd Annual Winter Conference of the American Assn. of Community Psychiatrists, Charleston, SC.

11-88 "Instrumentation of Drug-Induced Movement Disorders." Presented to California state legislators, their aides, and advocates of national mental health groups (NAMI and NARSAD).

08-88 "Classical Cases in Schizophrenia", with JA Talbot, MD, Professor and Chair, Department of Psychiatry, University of Maryland. Program produced with an educational grant from Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.

08-88 "Drug-Induced Extrapyramidal Syndromes in Psychiatric Patients." Texas State Hospital medical staff, Big Springs, TX.

06-88 "Role of Psychopharmacology in the Treatment of the Chronic Mental Patient." Department of Corrections at the California Medical Facility in Vacaville, CA.

04-88 "Psychosocial Rehabilitative Treatment of the Chronic Schizophrenic Patient." Presented to the staff of the Roseburg VA Medical Center, Roseburg, OR.

03-88 "Behavioral Rehabilitation of the Chronic Mental Patient." Workshop presented at the First Annual Winter Conference of the American Society of Community Psychiatrists, Colorado Springs, CO.

01-88 "Electromechanical Characteristics of Tardive Dyskinesia." The Biannual Winter Workshop on Schizophrenia, Badgastein, Austria.

10-87 "Medication/Consent." Symposium with Drs. R Liberman, J Vaccaro, and J Kane, presented at the 1987 Institute on Hospital and Community Psychiatry, Boston, MA.

09-87 "Medication Management and Patient Education." Annual Department of Mental Health Conference at Michigan State University, East Lansing, MI.

05-87 "Quantitative Assessment of Extrapyramidal Symptoms and Involuntary Movement," presented at a symposium on Acute and Chronic Extrapyramidal Symptoms and Tardive Dyskinesia, at the Annual Meeting of the APA, Chicago, IL.

10-86 "The Affective Disorders Spectrum," presented to the Graduate School of Psychology of the California Lutheran College in Thousand Oaks, CA.

04-86 "Unique Issues of Older Adults with Chronic Mental Health Problems, Focus on Schizophrenia." Mental Health and Aging Conference in Los Angeles, CA.

02-86 "The Geriatric Patient with Cardiac and Psychiatric Problems: Pharmacologic Concerns." VA Nursing Service for their Continuing Education Series in Los Angeles, CA.

10-85 "Psychopharmacologic Treatment of the Geriatric Population," presented to the Psychology interns at the VA as part of their Continuing Education Series in Los Angeles, CA.

Publications

Articles

98. Murphy D, Bailey K, Stone M, Wirshing WC. Addictive potential of quetiapine. *Am J Psychiatry.* 2008 Jul;165(7):918.
97. Tabibian JH, Wirshing DA, Pierre JM, Guzik LH, Kisicki MD, Danovich I, Mena SJ, Wirshing WC. Hepatitis B and C among veterans on a psychiatric ward. *Dig Dis Sci.* 2008 Jun;53(6):1693-8.
96. Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry.* 2007 May;68(5):705-10.
95. Buckley PF, Wirshing DA, Buchan P, Pierre JM, Resinck SA, Wirshing WC. Lack of insight in schizophrenia: impact on treatment adherence. CNS Drugs. 2007;21(2):129-41.
94. Wirshing DA, Pierre JM, Wirshing WC, Guzik LH, Resinck SA, Goldstein D, Zorick TS: Community re-entry program training module for schizophrenic inpatients improves treatment outcomes. *Schizophr Res.* 2006 Oct;87(1-3):338-9.
93. Meyer J, Loh C, Leckband SG, Boyd JA, Wirshing WC, Pierre JM, Wirshing DA: Prevalence of the metabolic syndrome in patients with schizophrenia. *Journal of Psychiatric Practice* 2006; 12(1): 6-10
92. Wirshing DA, Smith RA, Erickson ZD, Mena SJ, Wirshing WC: A wellness class for inpatients with psychotic disorders. *Journal of Psychiatric Practice* 2006; 12(1): 24-29
91. Pierre JM, Peloian J, Wirshing DA, Wirshing WC, Marder SM. A placebo controlled trial of modafinil for negative symptoms in schizophrenia. *Schizophrenia Bulletin* 2005; 31:501
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89. Pierre JM, Wirshing DA, Wirshing WC: High-dose antipsychotics: desperation or data-driven? *Current Psych* 2004, 3(8): 31-37.
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84. Pierre JM, Wirshing DA, Wirshing WC: "Iatrogenic malingering" in VA substance abuse treatment. *Psychiatric Services*, 2003, 54(2): 253-4

83. Wirshing DA, Wirshing WC: Aripiprazole: a viewpoint. *CNS Drugs*, 2002,16(11): 779-786

82. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose, and lipid levels. *J Clin Psychiatry 2002*; 63: 856-865

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- Pierre JM, Wirshing DA, Wirshing WC: Reply to: In response to Furst et al, "possible association of QTc interval prolongation with co-administration of quetiapine and lovastatin." *Biological Psychiatry* 2002; 52: 911-915.

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Updated—20 Mar 08

William C. Wirshing, M.D. Date

William C. Wirshing, M.D.

Educational and Professional Background

Education
I graduated in 1978 from the College of Engineering at the University of California at Berkeley with highest honors (cumulative G.P.A. 3.93) and a Bachelors of Science degree in Electrical Engineering and Computer Science (minor in bioelectronic systems). During my tenure there, I was elected to membership in the Phi Beta Kappa and Tau Beta Pi honor societies. The former is traditionally reserved only for those pursuing a "liberal" educational experience (e.g., College of Letters and Science) and the latter is the equivalent entity for students in the science-intensive curriculum of the School of Engineering. Although I then began medical school at UCLA almost immediately following my undergraduate studies, my education was interrupted when my youngest brother developed and then succumbed to brain cancer during my first and second years. During several lengthy arranged absences from school in southern California, I assisted my mother in caring for my brother and worked as an engineer in Mountain View (i.e., "Silicon Valley") California through the beginning of my third year at UCLA.

I completed my undergraduate medical schooling ("on time", despite my protracted absences from campus) with a 3.97 GPA and was given the Sandoz award for "Excellence in the Behavioral Sciences" at graduation in 1982. In addition, I was elected to the Alpha Omega Alpha Medical Honor Society at the end of my third year. I remained at UCLA for both my rotating internship during which I focused on internal medicine, neurology, and pediatrics and for my three-year residency training in psychiatry. My final year of residency training I was the Chief Resident in Geropsychiatry at the West Los Angeles Veterans Affairs Medical Center. Over the next two years, I was a Post Doctoral Research Scholar at UCLA, a fellowship position through the National Institute of Mental Health during which I learned and applied clinical research techniques for the study of persons with severe schizophrenia. My mentors were Professors Van Putten, Goldstein, and Marder.

Clinical, Research, and Teaching Background
I remained at both UCLA and the affiliated West Los Angeles Veterans Affairs Medical Center until late in 2006. Over the two decades between 1986 and 2006 though, both my clinical work and research focus remained on the treatment of persons with schizophrenia. I was the Chief of the Schizophrenia Treatment Unit at the VA Medical Center during the vast bulk of this epoch, and was also the Co-Chief of the Schizophrenia Outpatient Research Clinic during the last ten years. Though I rose through the traditional academic ranks at UCLA and even reached the level of full Professor over five years ahead of "schedule", I never lost my fascination with clinical care and never traded it for more administrative tasks as my career wandered through the decades. Since leaving the traditional ranks of academia, I have been able to continue and even expand my dual interests in clinical work and teaching. Over the last year I have been Vice President in charge of research and continuing medical education for Exodus Inc. in Culver City, CA and also Clinical Director of Exodus Real Recovery in Agoura Hills,

CA. In a typical month, I now see approximately 325 new patients; supervise nearly a dozen psychology doctoral candidates; and teach over a dozen nursing, social work, and nurse practitioner students. Over the course of my career, I have taken care of over twenty five thousand patients, the vast majority of which have suffered from one or another psychotic illness.

As is usual among clinical academicians, my patient care tasks and research interests dovetailed consistently and have always taken place in a setting with medical trainees at every level of experience. Teaching these persons over the years has been the third major leg of my vocational life. Unlike most of my academic colleagues, I never thought of these teaching duties as on obligation to be tolerated and where possible shunted to my younger colleagues. In fact, it generally occupied the top spot in my personal emotional ranking of our traditional tasks (i.e., teaching, research, and patient care). My teaching has been honored over the years with several awards from both my students and colleagues, including 2006 when I was again nominated for the Golden Apple Award by the graduating medical school class (the highest teaching accolade in the School of Medicine). I currently give over 125 routine lectures per year at my various work sites.

Within the context of these various positions and responsibilities, I have been able to experience, study, and then teach others about the care of seriously mentally ill patients. While I have been most consistently compelled by and fascinated with the prototypic psychotic illness schizophrenia, persons with bipolar illness (i.e., "manic depressive disorder") have taken up a close second place over the years. Like any academician in my area, I have sought and received grants to continue my studies and have published in the peer reviewed literature (with the substantial aide of my colleagues and assistants—see my attached CV for the details). I believe that I have been fortunate in the extreme to have had these professional opportunities. They have permitted me to live an enviable work life that I was never able to master and was therefore neither predictable nor routine.

Experience With Industry

These sundry positions also brought me into contact with the pharmaceutical industry that coincidentally became increasingly interested in the treatment of psychotic persons at the very onset of my career in the mid 1980's. This time marked the beginning of the second significant epoch of pharmacologic treatment of psychosis (The first one having begun in the early 1950's but which had plateaued by the late 1960's). This period saw the development, testing, and subsequent marketing of what came to be known as the "Second Generation" or "Atypical" antipsychotic compounds. Though not truly revolutionary or even novel per se (see below), they did constitute a significant advance in many, though not all, aspects over the older medications. This mutual interest in the treatment of psychosis allowed me to "test" potential medications in my patients under controlled protocol conditions from the beginning of their development by industry. Although not every medication that we tested over the years survived the gauntlet of clinical testing, we were able to test every medication that did receive the approval to market by the Food and Drug Administration.

The approval process for medications is a lengthy one that has become increasingly burdened by regulation and requirements over the years. As a consequence, it can take years for a given compound to move from first testing in patients to full marketing approval. Among the medications that we tested and studied that went on to receive approval have been risperidone (approval 1994), olanzapine (1996), ziprazadone (2000), aripiprazole (2002), and quetiapine (1997). The early and prolonged nature of this experience allowed us to develop a clinical knowledge of the real world effects of these drugs that was often at the very forefront of the entire field. As is usual with pharmacologic compounds, our novel discoveries and observations generally involved the toxic effects rather than the therapeutic impacts of the drugs.

In the early to mid 1990's we were among the very first to report on the curious metabolic effects. In particular, we noticed that many of our patients gained weight when first begun on these drugs and at a rate that was, on occasion, singular in our experience. We also noted that these patients soon began to suffer the usual downstream consequences of gaining weight (e.g., glucose intolerance, frank diabetes, and even severe hyperglycemia with resultant hyperosmolar coma). As is customary in the academic world, we described our experience in the peer reviewed literature and reported it at any number of scientific meetings. In addition, though, we worked with industry to extend, understand, and hopefully find ways to remediate these various toxicities. The increasingly high economic stakes of the field sometimes lead those in industry to confuse the message and the messenger (at least from my perspective). As a consequence, our relationships would, or at least could, sour and blossom suddenly, depending on the details of our latest report. As one might expect, our observations and conclusions were not infrequently challenged by one company only to be embraced and promoted by its competitor.

I did not have any direct dealings with Imperial Chemical Industries, as Zeneca was called prior to their name change, while they were developing their antipsychotic compound ICI 204636 (quetiapine's "name" prior to its receiving a formal designation by the nomenclature committee). I was, however, very familiar with the published preclinical and clinical literature on the drug in the 1980's and early 1990's. Immediately after launch in the United States in 1997, I began to lecture for the company and started negotiations with them to perform a high dose clinical trial in a subpopulation of persons with schizophrenia whose symptoms were unresponsive to other available antipsychotic compounds. While a variety of regulatory, legal, and logistical impediments conspired to ultimately thwart my hopes for such a trial, our interest in and experience with high dose treatment did result in a single publication (Pierre, et al, 2005). I continued to lecture and provide ad hoc consultation at the company's request (the last time was August of 2008), though the frequency of these interactions has diminished considerably over time. I have, however, kept them apprised of my concerns about and observation of their drug, including this last spring when I sent them a prepublication copy of a letter that was recently published in the American Journal of Psychiatry (Murphy, et al, 2008). Through out this lengthy association, I would characterize our relationship as mutually respectful and professionally cordial. In notable contrast to some of their corporate peers in the pharmaceutical industry, Astra Zeneca never treated

me dismissively or disrespectfully simply because I would describe an observed toxicity or express an unflattering opinion about quetiapine's clinical characteristics.

History of Antipsychotic Drugs

It can, I think, be persuasively argued that the origins of the "modern" biological theories of psychiatry can be traced directly to the serendipitous discovery of antipsychotic medications in the early 1950's. During that epoch, a trio of French physicians (psychiatrists Delay and Deniker and neurosurgeon Henri Laborit) determined that the experimental Rhône-Poulenc compound RP 4609 (i.e., chlorpromazine or "Thorazine") had a singular power to reduce psychotic symptoms in chronically and severely ill patients with schizophrenia. Schizophrenia is the prototypic psychotic illness that consistently afflicts 0.9 percent of the population, is life long and incurable, runs in families, and generally has its origins in late adolescence or early adulthood. It is further the exclusive province of the human animal—even our closest primate relatives do not develop schizophrenia. It would be difficult to overstate the magnitude of this pharmacologic discovery, coming as it did at a time when wet wraps, hydrotherapy, and frontal lobotomies were the only "effective" palliative treatments. The pharmacologic efficacy of chlorpromazine, though, came with an apparently obligatory neurotoxicity that developed after about two weeks of treatment. This neurotoxicity, which came to be called extrapyramidal symptoms or EPS, included parkinsonism (i.e., slowed movements and mentation, a specific tremor, and muscular rigidity), akathisia (i.e., an intensely dsyphoric sense of restlessness), and dystonia (i.e., sustained, uncontrollable, and functionally disruptive muscular contractions). While these acute EPS could be dramatic and overwhelming, they were transitory and would eventually disappear once the offending agent was discontinued. Unfortunately, there also developed a later, sometimes grotesque disorder of excessive motor movement that was termed tardive dyskinesia (literally "late bad movement"). It was eventually observed that this tardive dyskinesia (TD) would accrue with each passing year of cumulative exposure to the medication at a rate of three to five percent of the treated population per annum. More ominous still was the observation that unlike acute EPS, TD proved to be lifelong and irreversible in a large number of those afflicted (circa 50%), even if the causal agent were permanently discontinued. These neurotoxicities were so consistent, predictable, and uniform that they eventually came to be seen as the hallmark of this class of medications which were termed "neuroleptics" (i.e., "to seize the neuron"). In other words, these antipsychotic medications were defined quite literally by the toxicities they produced.

Though these EPS were the clinical bane of antipsychotic compounds, they were a crucially exploitable characteristic for drug developers. Because there is no animal model for schizophrenia per se, it is not possible to screen potential molecular candidates for this property. There are, however, many excellent animal models for EPS and related behavioral toxicities. It was thus possible to search for potential antipsychotic compounds by simply screening for extrapyramidal liability in one or another of these models. It should come as no surprise then that all antipsychotic medications shared the neurotoxic characteristic—it was this toxicity that allowed them to be discovered in the first place. Arvid Carlsson and colleagues detailed the mechanisms that are believed to underlie this duality (i.e., antipsychotic potential and neurotoxic liability) in the early

1960's. In a series of clever animal experiments and brilliant deductions he proposed that antipsychotics exerted both effects by binding to and blocking dopamine receptors (more specifically the D2 receptor subtype) in the brain. It is of historical note that he shared psychiatry's first Nobel Prize for Medicine in 2000 for these discoveries.

As an ultimate consequence of this process, there came to clinical market an array of often times chemically dissimilar compounds that had equipotent antipsychotic efficacy and were uniformly neurotoxic. They did, of course, vary in a number of secondary characteristics (e.g., anticholinergic potency, sedative potential, tendency to induce orthostatic hypotension, etc.), but their primary efficacies and core toxicities were effectively equivalent. It is important to note that these dopamine receptors are important not only in motor control and psychotic symptoms, but they are also crucial in mediating reward learning. Thus, any antipsychotic molecule that blocks these dopamine receptors will attenuate and possibly destroy an animal's (or a person's) ability to normally experience pleasure. In clinical practice these drugs are notoriously dysphorogenic and exceedingly difficult to subjectively tolerate.

The singular exception to these generalizations about antipsychotics is the compound clozapine. This molecule is a modified structural analog of the tricyclic antidepressant imipramine (a revolutionarily useful and powerful antidepressant medication that has no antipsychotic power whatsoever) and was synthesized by Sandoz Pharmaceuticals in 1959. Though its road to market was torturously long and marred by a number of tragically toxic detours, it ultimately proved itself to be a truly different antipsychotic. It was eventually shown that clozapine had greater antipsychotic power than conventional neuroleptics (as the rest of the antipsychotic market came to be named) and at ordinary antipsychotic doses it failed to cause the EPS that characterized its conventional counterparts. Clozapine then became the prototypic "atypical" antipsychotic in that it alone was a non-neuroleptic antipsychotic: a drug capable of separating antipsychotic efficacy from neurotoxic liability. While a number of often clever and sometimes even compelling explanations of how clozapine is able to exert these clinical behaviors have been elaborated, none have to date been proven. In addition, though the group of more recently developed and marketed antipsychotics (i.e., risperidone, olanzapine, quetiapine, aripiprazole, and ziprazidone) have claimed kinship to clozapine by usurping its "atypical" label, none has matched clozapine's antipsychotic power and all are variably more neurotoxic. This is not to say that as a "class" they have failed to improve upon the conventional compounds, but only that they have not succeeded in truly inheriting clozapine's legacy.

Quetiapine's Development

Imperial Chemical Industries first elaborated what they designated ICI 204636 in the early 1980's. It is a structural analog of clozapine and technically considered a dibenzothiazepine. Its receptor (i.e., the proteinaceous components on the lipid neural membranes of the central nervous system [CNS]) binding profile indicates that it has weak and easily reversible affinity for the classic D2 receptor that Carlsson identified in 1963. It also binds with weak to moderate intensity to a wide spectrum of other receptors in the CNS, but in a pattern that is really unlike any other antipsychotic compound,

including clozapine, upon which its structure is based. These other binding characteristics are conceptualized to account for quetiapine's observed clinical effects. In brief, they confer on quetiapine: sedation, low EPS liability, minimal impact on prolactin, orthostatic hypotension (i.e., a fall in blood pressure when standing), anticholinergic toxicity (i.e., constipation, dry mouth, blurred vision, memory disturbances, and tachycardia), and weight gain liability. All of these ultimately observed characteristics would be expected based only on the neuromolecular characteristics of quetiapine.

Though the knowledge of quetiapine's unique receptor binding profile allowed for the easy prediction of its pattern of toxicity in humans, its low and weak affinity at the critical D2 receptor posed a challenge for protocol designers during its early years of clinical testing. For all conventional compounds the appropriate dose to achieve optimal antipsychotic activity is exactly the dose that also begins to produce EPS. With an "atypical" drug though, the appropriate dose would be an unknown amount lower. Thus, an early hurdle for quetiapine was determining just where the optimal antipsychotic dose range was located. Ultimately quetiapine's FDA registration trials involved multiple doses (five) of quetiapine over a ten fold dosing range compared to single dose of the reference conventional neuroleptic haloperidol. Despite the methodologic asymmetry of this design that markedly favored quetiapine, it failed to beat its conventional comparator at any dose. In fact, the haloperidol arm was generally slightly better (though not statistically so) than any of the five doses of quetiapine. This pattern of being marginally equal to or slightly inferior to comparator drugs has been repeated numerous times over the years of testing. When AZ attempted to perform a meta-analysis (i.e., combining multiple trials to achieve greater statistical power in an effort to show a small effect that is not apparent in any single study) on its accrued dataset, they discovered this very pattern. This disappointing result prompted the marketing personnel within AZ to "spin" these conclusions by touting that quetiapine had "unsurpassed efficacy". While technically correct from a statistical point of view because no single study had shown that any conventional comparator was statistically superior to quetiapine, such hype is clearly disingenuous sophistry.

When considered across many trials involving schizophrenic subjects, quetiapine has been demonstrated to be about 10-20 percent less effective than standard doses of conventional medications. This was shown most clearly in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that was reported in late 2005. This NIMH funded trial compared four atypical medications (quetiapine, ziprazidone, risperidone, and olanzapine) to a single typical medication (perphenazine) and involved 1460 subjects treated over an 18-month epoch. The primary outcome variable was "time to discontinuation" of the assigned drug. The results revealed that quetiapine was about 20 percent less effective than the conventional agent perphenazine (4.6 vs. 5.6 months) and about 50 percent less effective than olanzapine (9.2 months).

While these efficacy facts were disappointing and clearly contributed to quetiapine's dismal market share when it was first approved for use in 1997, it also suggested to me a tantalizing possibility. Because conventional antipsychotic medications were all

essentially equi-efficacious and seemed to share a single underlying mechanism of action, any drug that had demonstrably less efficacy might possibly work through a dissimilar mechanism. This possibility was a major motivating factor in my wanting to pursue a higher than standard dose experimental trial with the company after the drug was launched. I continue to believe that quetiapine does, in fact work through largely distinct mechanisms. Unfortunately this distinction translates into slightly less pharmacologic power on average than conventional medications. AZ has "oversold" quetiapine's efficacy in their marketing endeavors for years.

Quetiapine's Toxic Metabolic Profile

The dataset that Zeneca had compiled on quetiapine prior to its launch in 1997 clearly indicated that clinically significant weight gain was a common side effect of quetiapine. The data from Zeneca's Phase II/III trials demonstrated a clear dose related impact on weight that compellingly worsened over time. Using the FDA's definition of clinically pertinent weight gain (i.e., a 7% increase), quetiapine routinely impacted over 25 percent of the treated population (somewhat lower for lower doses of quetiapine and somewhat higher with higher quetiapine doses). The average shift in weight was 6.2 lbs over the first six months of treatment and 11 lbs after six months of treatment. This is approximately halfway between the weight gain induced by risperidone and olanzapine—quetiapine's major competitors at launch. Weight gains of this magnitude are impressively large and impact an amazingly large and consistent percentage of patients. Despite these data, which have been available to the company since before launch, the label for quetiapine has never, even to the present day, "warned" of this predictable and serious toxicity. Instead, the label has merely listed in the adverse experiences section that quetiapine is "sometimes associated with increases in body weight". Further, their marketing materials over the years have consistently touted that quetiapine is "weight neutral". This is palpably inappropriate and inadequate at best and deceptively misleading at worst. It is my opinion that this labeling deficiency rises to the legal definition of gross negligence (i.e., "willful disregard for the safety of others"). It is unconscionable that after more than a decade's time that the warnings section is still silent about the single most prominent serious toxic characteristic of the compound.

There are a number of well-known health consequences to increases in adiposity. Among these are increased risks for glucose intolerance and even frank diabetes, increases in total cholesterol and triglycerides in the blood, secondary risks for cardiovascular disease, increased rates of degenerative osteoarthritis, and even increased risks for certain malignancies (e.g., colon cancer). The fact that quetiapine use results in weight gain and therefore causes diabetes in susceptible patients cannot be rationally disputed. This was confirmed by the APA/ADA consensus conference on the metabolic toxicities of the atypical antipsychotics held in 2004. That conference of independent (i.e., non-industry) experts (at which I provided the presentation on the monitoring protocol) concluded that quetiapine use could result in significant weight gain, increased rates of diabetes, and pathologic changes in lipid profiles. Although the current label change implemented in 2007 does direct one to a new section in the adverse events section that documents, to a degree, some of the measured increases in new onset diabetes, it remains inadequate and misleading. Firstly, the "class labeling" warning section on endocrinologic toxicities is

laced with generalities, disclaimers, and distracting verbiage. It fails completely to state the measured increases in new onset diabetes that are specific to quetiapine and that are detailed in the adverse experiences section. Secondly, it fails to make the known connection between increases in adiposity and subsequent changes in glucose regulation. It gives the mistaken impression that the risks of diabetes only apply to a decidedly minor (circa 2-4%) portion of treated patients when, in fact, nearly one third of patients treated with standard doses for as little as a year are at decidedly increased risk of glucose disregulation. The company personnel have opined in depositions that the details of quetiapine's measured risk of diabetes and related endocrinologic disturbances were unknown until the results of these later done studies were completed. Such rhetoric is intellectually and clinically dishonest as it requires one to deny the clinical fact that increases in adiposity that are caused by quetiapine (and were known to the company before launch in 1997) will result in predictable increase in endocrinologic dysfunction. It is axiomatic that increases in obesity will result in subsequent increases in hyperglycemia, frank diabetes, hyperosmolar coma, and even death due to endocrinologic complications. To deny otherwise, as AZ officials continue to do to the present day, is negligently irresponsible.

Additionally, the label is virtually silent (or at least it is decidedly unclear) about quetiapine's ability to induce massive changes in circulating triglycerides and thereby lead to secondary and potentially lethal pancreatitis (i.e., marked inflammation of the pancreatitis). When a person gains significant adiposity, there is a predictable increase in the levels of circulating lipid pools (i.e., triglycerides, VLDL, LDL, etc.) because to body must manage a larger flow of fats from the gut and to and from the tissues. These changes, while potentially of long-term clinical pertinence, are usually of ordinary magnitude. Quetiapine, though, also results in massive acute elevations in triglycerides that can, on occasion, overwhelm the body's fat management system and cause secondary pancreatitis. The precise mechanisms whereby this toxicity is mediated have yet to be elucidated, however, it is likely that interference with one of the early lipid management enzymes in the liver (e.g., lipoprotein lipase A) causes a "backup" of the triglyceride transport vehicle (i.e., chylomicrons) from the gut that leads to the hypertriglyceridemia. This additional metabolic-like toxicity is unrelated to changes in weight, tends to occur during the first several months of treatment, and is markedly more acutely serious than the more pedestrian increases in the sundry lipid pools that predictably follow increases in adiposity. This toxicity has clearly emerged during the post marketing surveillance period, has been reported frequently in the case report literature, and was discussed at length at the consensus conference in 2004.

Addictive Potential

The single most consistent toxic effect of quetiapine is sedation. This property when coupled with quetiapine's low EPS profile has prompted clinicians to use the drug excessively off-label for such conditions as anxiety and insomnia. These characteristics also raise a reasonable concern that quetiapine may have some addictive potential. In fact clinical experience and a number of case reports have suggested that certain patients will abuse, divert for sale, and become physically dependent on quetiapine (Pierre, et al,

2004; Murphy et al, 2008). Despite these facts the label has been virtually silent about this reality.

Off Label Use

Quetiapine has come to dominate the atypical antipsychotic market primarily because it is used excessively off label (current estimates are about two thirds of the prescriptions are off-label). I am of the opinion that primary among the reasons for this disproportionate off label use are the facts that quetiapine is sedating and highly subjectively tolerable and the inaccurate clinical impression that it is also comparatively free of concerning toxicities and devoid of abuse potential. A secondary reason is that quetiapine's share of the on label market is reduced because it is simply not as potent an antipsychotic as other available products. While prescribing a drug for off label use is a common and often clinically reasonable practice, promoting a drug for off label use is illegal. AZ was clearly aware of the excessive off label use of quetiapine over the years. Their officials have stated repeatedly in depositions that AZ endeavored to provide label support of these "passively observed" prescriptive habits by investing heavily in confirmatory studies. Though many such studies were performed, I consider the claim largely dishonest. If true, then it would have been imperative for AZ to study the largest and most excessive off label use, to wit, insomnia. Such a study would have been logistically and economically trivial to perform, at least in comparison to the studies done in mood and psychosis based disorders. There is to date no evidence of any quality that demonstrates that quetiapine decreases sleep latency, increases total sleep time, normalizes sleep architecture, or improves daytime wakefulness. There is, in fact, ample evidence that quetiapine impairs significantly daytime wakefulness. I believe that AZ knew that any real detailed sleep study would ultimately be an indictment of clinical practice and would potentially cut the total use of their product by more than half. It is further my opinion that AZ mischaracterized the true toxic potential of their product and that this behavior has in part prompted clinicians to use their product inappropriately and excessively off label. If clinicians had been aware of the true metabolic toxicities and addictive liabilities of quetiapine then I do not believe that we would have the amount of off label usage we see today. It is my opinion therefore that AZ has been engaged in "indirect" off label marketing. While their behavior may have in fact been technically within the "letter of the law", it was and continues to be irresponsible, improper, and ethically indefensible.

Conclusions/Summary

AZ's marketing of quetiapine has consistently exaggerated the true efficacy of the compound.

AZ has been aware of the true metabolic toxicities of quetiapine since before launch in 1997. Despite this they have engaged in a marketing campaign that has minimized, obfuscated, or frankly denied these metabolic realities. Their product label has been consistently and continuously inadequate in its warnings about the impact on lipid and glucose metabolism, hyperglycemia, and diabetes. Their label continues to be wholly inadequate to the point of being decidedly misleading in its warnings about weight gain.

Additionally, the current label is inadequate regarding quetiapine's ability to markedly disrupt normal lipid metabolism and cause massive hypertriglyceridemia and secondary pancreatitis.

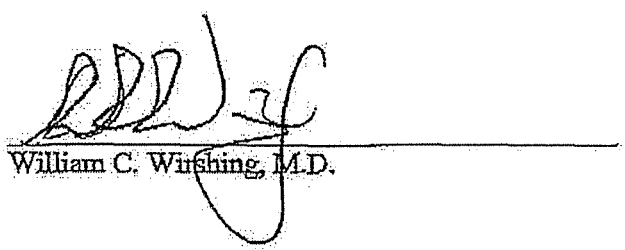
The current label is inadequate in its description about the abuse potential of quetiapine. AZ should have identified and warned of this abuse liability based on the clinical characteristics of quetiapine and the curious and excessive off label use patterns. Further, their tacit acceptance of the excessive use of their product for routine insomnia for the past decade without ever having investigated the effects of their product on sleep, is tantamount to passive marketing for an off label indication. This failure to investigate has been compounded by their insistence that they have behaved responsibly by investing heavily in research to establish on label support for the prescriptive patterns they knew to exist.

AZ's behavior has given prescribing clinicians an inaccurate impression of quetiapine's toxic profile and addictive potential which has robbed physicians of the ability to make informed risk/benefit analysis prior to prescribing quetiapine to a patient. This has led in part to the excessive and inappropriate off label use of the product and to injury and damage to patients who would not have otherwise ever received the medication.

My opinions as stated in this report are based on my education, training, and experience and my review of the relevant literature, internal Astra Zeneca documents, corporate depositions, and public documents and are stated to a reasonable degree of medical probability. It is my understanding that discovery is ongoing and I thus reserve my right to supplement or expound upon my opinions pending review of additional information.

My fees for work in this litigation are $500 per hour.

A list of my testimony for the past 4 years is attached.



William C. Wirshing, M.D.

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prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.

- You should not become pregnant when taking NOLVADEX or during the two months after you stop taking it as NOLVADEX may harm your unborn child. Please contact your doctor for birth control recommendations. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX.

What should I avoid or do while taking NOLVADEX?

- You should contact your doctor immediately if you notice any of the following symptoms. Some of these symptoms may suggest that you are experiencing a rare but serious side effect associated with NOLVADEX (see **"What are the possible side effects of NOLVADEX?"**).
  - — new breast lumps
  - — vaginal bleeding
  - — changes in your menstrual cycle
  - — changes in vaginal discharge
  - — pelvic pain or pressure
  - — swelling or tenderness in your calf
  - — unexplained breathlessness (shortness of breath)
  - — sudden chest pain
  - — coughing up blood
  - — changes in your vision

  If you see a health care professional who is new to you (an emergency room doctor, another doctor in the practice), tell him or her that you take NOLVADEX or have previously taken NOLVADEX.
- Because NOLVADEX may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medicines. Be sure to tell your doctor if you are taking warfarin (Coumadin) to thin your blood.
- You should not become pregnant when taking NOLVADEX or during the 2 months after you stop taking it because NOLVADEX may harm your unborn child. You should see your doctor immediately if you think you may have become pregnant after starting to take NOLVADEX. Please talk with your doctor about birth control recommendations. If you are taking NOLVADEX to reduce your risk of getting breast cancer, and you are sexually active, NOLVADEX should be started during your menstrual period. If you have irregular periods, you should have a negative pregnancy test before you start NOLVADEX. NOLVADEX does not prevent pregnancy, even in the presence of menstrual irregularity.
- If you are taking NOLVADEX to reduce your risk of getting breast cancer, you should know that NOLVADEX does not prevent all breast cancers. While you are taking NOLVADEX and after you stop taking NOLVADEX and in keeping with your doctor's recommendation, you should have annual gynecological check-ups which should include breast exams and mammograms. If breast cancer occurs, there is no guarantee that it will be detected at an early stage. That is why it is important to continue with regular check-ups.

What are the possible side effects of NOLVADEX?

Like many medicines, NOLVADEX causes side effects in most patients. The majority of the side effects seen with NOLVADEX have been mild and do not usually cause breast cancer patients to stop taking the medication. In women with breast cancer, withdrawal from NOLVADEX therapy is about 5%. Approximately 15% of women who took NOLVADEX to reduce the chance of getting breast cancer stopped treatment because of side effects.

The most common side effects reported with NOLVADEX are: hot flashes; vaginal discharge or bleeding; and menstrual irregularities (these side effects may be mild or may be a sign of a more serious side effect). Women may experience hair loss, skin rashes (itching or peeling skin) or headaches; or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough; however, hair loss is uncommon and is usually mild. A rare but serious side effect of NOLVADEX is a blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take NOLVADEX are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if NOLVADEX is stopped. Women may also have complications from treating the clot, such as bleeding from thinning the blood too much. Symptoms of a blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of a blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move to the lungs. If you experience any of these symptoms of a blood clot, contact your doctor immediately.

NOLVADEX increases the chance of having a stroke, which can cause serious medical problems, disability, or death. If you experience any symptoms of stroke, such as weakness, difficulty walking or talking, or numbness, contact your doctor immediately.

NOLVADEX increases the chance of changes occurring in the lining (endometrium) or body of your uterus which can be serious and could include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in the pelvis (lower stomach). These may be caused by changes to the lining (endometrium) or body of your uterus. It is important to bring them to your doctor's attention without delay as they can occasionally indicate the start of something more serious and even life-threatening.

NOLVADEX may cause cataracts or changes to parts of the eye known as the cornea or retina. NOLVADEX can increase the chance of needing cataract surgery, and can cause blood clots in the veins of the eye. NOLVADEX can result in difficulty in distinguishing different colors. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eyes) or hypertriglyceridemia (increased levels of fats in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen). Stop taking NOLVADEX and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking NOLVADEX for a long time.

If you are a woman receiving NOLVADEX for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting NOLVADEX and may be associated with a good response to treatment.

Many of these side effects happen only rarely. However, you should contact your doctor if you think you have any of these or any other problems with your NOLVADEX. Some side effects of NOLVADEX may become apparent soon after starting the drug, but others may first appear at any time during therapy.

This summary does not include all possible side effects with NOLVADEX. It is important to talk to your health care professional about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

How should I store NOLVADEX?

NOLVADEX Tablets should be stored at room temperature (68–77°F). Keep in a well-closed, light-resistant container. Keep out of the reach of children.

Do not take your tablets after the expiration date on the container. Be sure that any discarded tablets are out of the reach of children.

This leaflet provides you with a summary of information about NOLVADEX. Medicines are sometimes prescribed for uses other than those listed. NOLVADEX has been prescribed specifically for you by your doctor. Do not give your medicine to anyone else, even if they have a similar condition because it may harm them.

If you have any questions or concerns, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about NOLVADEX written for health care professionals that you can ask to read. For more information about NOLVADEX or breast cancer, call 1-800-34 LIFE 4.

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Shown in Product Identification Guide, page 306

SEROQUEL®

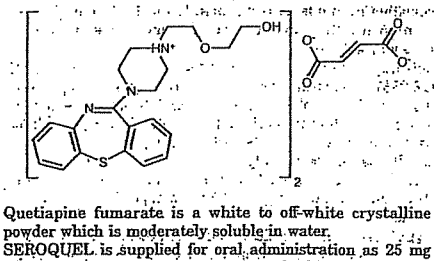
[serō-quēl]

(quetiapine fumarate)

TABLETS

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow), 200 mg (round, white), and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly *via* hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole.

Continued on next page

Seroquel—Cont.

Dose adjustment of quetiapine will be necessary if it is co-administered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION.**)

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION.**)

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (22/2162) of the patients treated with SEROQUEL, compared with 0% (0/206) on placebo and about 0.5% (2/420) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications).

Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see **Animal Toxicology**). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis.) Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5

day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION.**)

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

Table 1. Treatment-Emergent Adverse Experience Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

Body System/ Preferred Term	SEROQUEL (n=510)	Placebo (n=206)
Body as a Whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous System		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive System		
Constipation	9%	5%
Dry Mouth	7%	3%
Dyspepsia	6%	2%
Cardiovascular System		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and Nutritional Disorders		
Weight gain	2%	0%
Skin and Appendages		
Rash	4%	3%
Respiratory System		
Rhinitis	3%	1%

Continued on next page

Seroquel—Cont.

Special Senses		
Ear pain	1%	0%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

Dose Groups	Placebo	SEROQUEL 75mg	150mg	300mg	600mg	750mg
Parkinsonism EPS	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
incidence	16%	6%	6%	4%	8%	6%
Anticholinergic Medications	14%	11%	10%	8%	12%	11%

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: *Frequent:* hypertonia, dysarthria; *Infrequent:* abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; *Rare:* aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: *Frequent:* flu syndrome; *Infrequent:* neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; *Rare:* abdomen enlarged.

Digestive System: *Frequent:* anorexia; *Infrequent:* increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; *Rare:* glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: *Frequent:* palpitation; *Infrequent:* vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; *Rare:* angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: *Frequent:* pharyngitis, rhinitis, cough increased, dyspnea; *Infrequent:* pneumonia, epistaxis, asthma; *Rare:* hiccup, hyperventilation.

Metabolic and Nutritional System: *Frequent:* peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; *Rare:* glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: *Frequent:* sweating; *Infrequent:* pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; *Rare:* exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; *Rare:* gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; *Rare:* abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: *Frequent:* leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; *Rare:* hemolysis, thrombocytopenia.

Endocrine System: *Infrequent:* hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism.

*adjusted for gender

Post Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on

one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

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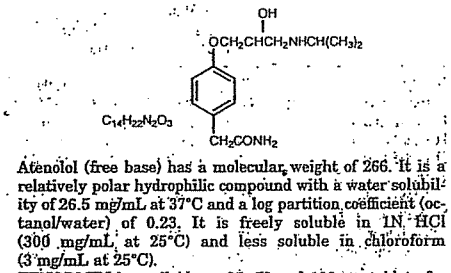
Shown in Product Identification Guide, page 306

TENORMIN® ℞
[ten-or-min]
(atenolol)
ONE TABLET A DAY

DESCRIPTION

TENORMIN® (atenolol), a synthetic, beta$_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. The molecular and structural formulas are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration.

Inactive Ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

CLINICAL PHARMACOLOGY

TENORMIN is a beta$_1$-selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, TENORMIN inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m^2. (See DOSAGE AND ADMINISTRATION.)

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of TENORMIN, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta$_1$ selectivity of TENORMIN has been shown by its reduced ability to reverse the beta$_2$-mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of TENORMIN producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, TENORMIN produced a significantly smaller decrease of FEV$_1$ than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, TENORMIN, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of TENORMIN is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of TENORMIN with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus TENORMIN (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of < 50 bpm or systolic blood pressure < 100 mm Hg, or with other contraindications to beta blockade were excluded. Thirty-eight percent of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the TENORMIN group were to receive TENORMIN I.V. Injection 5-10 mg given over 5 minutes plus TENORMIN Tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either TENORMIN Tablets 100 mg once daily or TENORMIN Tablets 50 mg twice daily on days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first-degree atrioventricular block at entry.

During the treatment period (days 0-7), the vascular mortality rates were 3.89% in the TENORMIN group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the P < 0.05 level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1%-27%. Most of the difference was attributed to mortality in days 0-1 (TENORMIN - 121 deaths; control - 171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

Atenolol Geriatric Pharmacology: In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

INDICATIONS AND USAGE

Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

TENORMIN is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending car-

Continued on next page

EXHIBIT 44

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION	**MDL DOCKET NO.**
This document relates to:	**6:06-MDL-1769-ACC-DAB**
ALL CASES	

DECLARATION OF LAURA M. PLUNKETT, Ph.D., DABT

1. My name is Laura M. Plunkett. I am competent to make this declaration, and the facts stated herein are within my personal knowledge and are true and correct.

2. I am a pharmacologist, toxicologist, United States Food and Drug Administration ("FDA") Regulatory Specialist and principal of a consulting company known as Integrative Biostrategies, L.L.C. Based in Houston, Texas, Integrative Biostrategies is a consulting firm that works at the interface of biological science, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

3. I am board certified as a Diplomat of the American Board of Toxicology. I am a member of several professional organizations and have authored or coauthored numerous scientific publications. I have over 20 years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

4. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

5. From June 1984 through August 1986 I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory at the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

6. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduates students in pharmacology and toxicology as well as the neurosciences. During this time I studied drugs of all classes that affect brain function, including antipsychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions.

7. From December of 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically with the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career

(ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on current labeling regulations and generally acted as a regulatory affairs staff for small companies in early stages of product development. A tool common to all my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. I have attached hereto a copy of my curriculum vitae and the expert report I prepared for the Plaintiffs in this litigation, which are attached hereto as Exhibits A and B respectively, and incorporated by reference herein.

8. In my regulatory affairs experience and work with prescription drugs, as well as through my knowledge, skill, training, and experience as a pharmacologist, I am knowledgeable about the "warning" standard established in 21 C.F.R. § 201.57(e). That section requires that drug warnings "shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should have been taken if they occur." Importantly, "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." I am also knowledgeable of the fact that, by law, a prescription

drug "label" includes promotional and marketing materials associated with the drug as well as the "package insert" accompanying the drug's packaging.

9. Based on my knowledge, skill, training, and experience as a pharmacologist and toxicologist and in working with prescription drugs, I am further able to assess the risks associated with a particular drug and, in particular, identify whether the standard "reasonable association of a serious hazard with a drug" is consistent with information related to drug risks and hazards that was known or should have been known by the drug manufacturer. After my review and analysis of AstraZeneca company documents, as well as based on my review of peer-reviewed medical literature pertinent to Seroquel and other antipsychotics, I have formed the following opinions with respect to the adequacy—specifically the accuracy, clarity, and unambiguousness—of Seroquel's labeling from 1999 to present, premised on whether AstraZeneca provided a warning "as soon as there [was] reasonable evidence of an association of a serious hazard" with Seroquel.

10. Regarding the label/package insert accompanying Seroquel from 1999 to the present, studies that I have reviewed reveal that weight gain has long been identified as a serious side effect of anti-psychotic drugs. However, it has also been recognized more recently, according to the pertinent medical literature, that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain. When considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious health effects that pose a risk to a person's health, such as weight gain. Further, my review of AstraZeneca's own documents revealed that the company was aware of the propensity for Seroquel to cause rapid, clinically

significant weight gain. For example, 1997 internal correspondence that I have reviewed show that the company's "Study 15" indicated that weight gain was "rapid," "consistent," "clinically significant," "dose related," and "doesn't stop" during Seroquel treatment. Additionally, by 1999, Dr. Joyce Small, who conducted the company's "Trial 8" for Seroquel, wrote that because the second generation antipsychotics clozapine, olanzapine, and quetiapine "cause the most weight, these drugs may be most likely to induce diabetes." By 2000, AstraZeneca's Global Drug Safety Physician had stated in a company "Safety Position Paper" that there was "reasonable evidence" to suggest that Seroquel "can cause" diabetes, as Dr. Small predicted would result by Seroquel causing clinically significant weight gain. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

11. It is my opinion, therefore, that the 1999-present label/package insert with respect to weight gain is inaccurate, unclear, and ambiguous because the so-called "warning" of weight gain is not contained under the "Warnings" section of the label, but appears much further into the body of the label/package insert in the "Adverse Reactions" section—literally dozens of paragraphs after the "Warnings" section, which is near the top of the label. The weight gain information also fails to describe any of the serious, potentially life threatening side effects associated with weight gain—namely diabetes mellitus and hyperglycemia—of which AstraZeneca was aware. Because there existed reasonable evidence of an association with Seroquel and weight gain, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

12. Moreover, the promotional and marketing materials utilized by the company with regard to weight gain also constituted "label" information that were unclear, inaccurate, and ambiguous in part because they directly contradicted the information contained, for example, in the adverse reactions section of the package insert. For example, the materials that I have reviewed, including Dr. Brecher's 2000 article and Dr. Nasrallah's 2002 article, informed doctors that Seroquel did not cause weight gain or that Seroquel had a favorable weight profile. A handout discussing Dr. Reinstein's experiences with Seroquel in his patients, which I have reviewed, suggested that weight loss along with improvement of diabetes was a beneficial side effect of Seroquel. AstraZeneca has also repeatedly stated in sponsored literature and marketing material that I reviewed (such as the Nasrallah and Brecher articles) that there is not a dose-dependent relationship between Seroquel and weight gain. I have also reviewed other sales and marketing "messages" or "themes" that were used by AstraZeneca salespersons in direct contact with physicians during this same time period. Those "messages" or "themes" included claims that Seroquel is "weight neutral," or causes "minimal weight gain" or has a "favorable weight profile." The sales messages contradicted what AstraZeneca knew to be true about Seroquel and weight gain, but also ran counter to Seroquel's own Adverse Reactions section of the label/package insert, which showed (and still shows) that 23% of Seroquel users will experience clinically significant weight gain. For those additional reasons, Seroquel's "label" information regarding "weight gain"—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous with respect to warning about weight gain.

13. Regarding the label/package insert accompanying Seroquel from 1999 to 2004 concerning hyperglycemia and diabetes mellitus, studies that I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel can cause serious metabolic effects that adversely impact health including diabetes and hyperglycemia, effects that can even become life-threatening if not treated. Further, my review of AstraZeneca's own documents reveals that the company was aware of an association with Seroquel and hyperglycemia/diabetes since at least 1999, when Dr. Small recognized after Trial 8 that Seroquel and two other antipsychotic drugs caused the most weight gain and also were likely to cause diabetes. In 2000, as noted above, the company's Global Drug Safety Physician concluded that Seroquel can cause impaired glucose dysregulation including diabetes. In addition, by November 2002, the Japanese government had evidently reached a similar conclusion, requiring that AstraZeneca send a "Dear Doctor" letter to Seroquel prescribers informing them of the increased risk of diabetes and related complications and mandating that (a) Seroquel not be administered to patients with a history of diabetes; (b) patients treated with Seroquel be monitored carefully including measurement of blood glucose levels; and (c) information regarding the severe adverse reactions that may occur, including diabetic ketoacidosis and diabetic coma, must be fully explained to the patient and family. The above constitutes reasonable evidence of an association of a serious hazard with Seroquel.

14. It is my opinion, therefore, that the 1999-2004 label/package insert with respect to hyperglycemia/diabetes is inaccurate, unclear, and ambiguous because the so-called "warning" of diabetes and hyperglycemia is not contained under the "Warnings"

section of the label, but appears (again) in the "Adverse Reactions" section of the label/package insert. That section mentions the words "diabetes" and "hyperglycemia" once, and classifies those reactions as "infrequent." The diabetes and hyperglycemia risk is also distorted by the fact that "hypoglycemia" and "weight loss" are also listed as infrequently occurring adverse reactions. As the manufacturer of Seroquel, AstraZeneca was under a duty to revise the label as soon as there was reasonable evidence of an association with the serious health hazards of hyperglycemia and diabetes. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia and diabetes, and the company did not revise the label to clearly, accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

15. Moreover, the promotional and marketing materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this period also constitute "label" information that was unclear, inaccurate, and ambiguous because it too downplayed the severity of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, a study by Dr. Reinstein that was shown to, distributed to, and/or discussed with Seroquel prescribers, the integrity of which has since been discredited, implies that Seroquel patients lost weight and their diabetes was cured after taking Seroquel for ten weeks. For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

16. Regarding the label/package insert accompanying Seroquel from 2004 to 2007 concerning hyperglycemia and diabetes mellitus (the so-called "class warning"), studies that

I have reviewed reveal that, when considered as a whole in a weight-of-the-evidence assessment, the available scientific data indicate that Seroquel's effect on weight gain and blood glucose levels differed from some other members of the class of second generation anti-psychotics. Further, the class warning does not describe accurately or clearly the rate and severity of hyperglycemia and diabetes risk associated with Seroquel uniquely, as opposed to other second generation anti-psychotics generally. For example, studies and medical literature that I have reviewed indicate that Abilify and Geodon, two of Seroquel's competitors, are not associated with statistically significant weight gain or hyperglycemia/diabetes to the critical degree that Seroquel has such an association.

17. The warning contained on the 2004-2007 label simply states that hyperglycemia and diabetes "has been reported." The warning is also qualified by statements that elevations in the rates of occurrence of hyperglycemia/diabetes in the schizophrenic or general populations may be confounding factors. In addition, AstraZeneca documents that I have reviewed show the company was aware of this risk long before and during this time period. For example, before and during that time, other international regulatory bodies were requiring specific changes to Seroquel's product labeling related to risks of hyperglycemia and diabetes, but not to anti-psychotics generally—*e.g.,* the Japanese "Dear Doctor" letter. Additionally, in 2005, permission to market Seroquel in France was denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Because there existed reasonable evidence of an association with Seroquel and hyperglycemia/diabetes, and the company did not revise the label to clearly,

accurately, and unambiguously describe that risk as soon as the company became aware of the association, the warning is therefore inadequate.

18. Additionally, the marketing and promotional materials utilized by the company with regard to Seroquel and hyperglycemia and diabetes risks during this time also constitute "label" information that was unclear, inaccurate, and ambiguous because it minimized the severity and frequency of the risk of hyperglycemia and diabetes associated with Seroquel treatment. For example, I have reviewed AstraZeneca documents evidencing that the Reinstein study and the Brecher article were still being disseminated during this time period. In 2006, the FDA Division of Drug Marketing, Advertising, and Communications (FDA DDMAC) admonished the company because it had not satisfactorily disclosed information concerning hyperglycemia and diabetes risks—in accord with the then, current "class warning"—causing the FDA DDMAC to determine that the promotional materials were "misleading" and "undermined the warning." For those additional reasons, Seroquel's "label" information regarding hyperglycemia and diabetes—including the package insert and all sales and marketing materials—are inadequate because they are inaccurate, unclear, and ambiguous.

19. Regarding the label that now accompanies Seroquel, that label (which was revised in or about October 2007) still fails to accurately, clearly, and unambiguously warn of Seroquel's dangers relative to diabetes. Following the cross-reference contained in the "Warnings" section to the "Adverse Reactions" reactions section, one sees that "diabetes" is never mentioned in the Adverse Reactions section. However, the data contained in that section shows that, in two long-term clinical trials, Seroquel users exhibited diabetes-level

hyperglycemia more than two times as often as subjects taking placebo. The fact that the Warnings section itself does not mention the disturbing rate with which Seroquel is associated with diabetes renders the warning patently unclear, inaccurate, and ambiguous.

20. The shortcomings of the Warnings section are exacerbated by the Adverse Reaction section's characterization of diabetes-level hyperglycemia as merely "hyperglycemia" and "increased blood sugar." (Fasting blood glucose $\geq$ 126/mg/dl or non-fasting blood glucose $\geq$ 200/mg/dl, as identified in the Adverse Reactions section, is diabetes, not merely "hyperglycemia," according to my knowledge, training, and review of the medical literature identified in my report.). Furthermore, I have reviewed an AstraZeneca internal document in which Seroquel's risk of diabetes-level blood glucose dysregulation is characterized as "common." Because there exists reasonable evidence of an association with Seroquel and diabetes, yet the company failed to revise the label to state the risk of "diabetes" rather than simply "hyperglycemia," the company did not revise the label as required, and it is therefore inaccurate, unclear, and ambiguous.

21. I have reviewed June 2008 FDA correspondence to AstraZeneca regarding the 2007 label indicating that the FDA also deems the current label inadequate. The FDA has requested that AstraZeneca modify the information in the Adverse Reactions section to explain potential design limitations in the studies from which the data mentioned in the above paragraph was drawn. The FDA states that the more than two-fold increase in Seroquel patients contracting diabetes over placebo patients in the studies should be clarified by linking the same to "[t]he mean change in glucose from baseline," which "was +5.0 mg/dl for SEROQUEL and -0.05 mg/dl for placebo," a more than five-times greater increase. The

FDA also requested that AstraZeneca state that the blood glucose data may be "underestimated" because of the fact that the studies pre-screened participants who could not tolerate Seroquel (including, for example, because of high blood glucose readings) in the open-label phase prior to randomization, effectively dropping those intolerant participants from the studies, and skewing the results in AstraZeneca's favor. After reviewing the current package insert on the Seroquel.com website at the time of executing this Declaration, AstraZeneca has still not adhered to the FDA's request to change the current label as described. For those additional reasons, Seroquel's current label is inadequate because it inaccurately, unclearly, and ambiguously states the risk of diabetes with Seroquel.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 21st day of November, 2008.

Laura M. Plunkett, Ph.D., DABT

CURRICULUM VITAE

Laura M. Plunkett, Ph.D., D.A.B.T

OFFICE ADDRESS 1223 Melford Drive
Houston, TX 77077-1544

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

President. Integrative Biostrategies (IB) LLC, 2001- present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia, College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Diplomate, American Board of Toxicology, 1993 to present.

Registered patent agent, 1999.

PROFESSIONAL MEMBERSHIPS

Member, Society for Toxicology 1992 - present

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Counselor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 - present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 - present

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1. **Plunkett LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Florida A&M University, Tallahassee, FL, October 26, 2006.

2. **Plunkett LM.** The guidance as currently implemented: experience with Minnesota's draft risk levels. Presented at the ISRTP workshop entitled: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures. Genotoxic Mode of Action and Implications for Human Health-Based Standards. Baltimore, MD February 10, 2005.

3. **Plunkett LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 17, 2004.

4. **Plunkett LM.** Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

5. **Plunkett LM.** A Road map to the US Food And Drug Administration Regulations. Invited Speaker and Session Co-chair, Federation of European Biochemical Societies (FEBS), Istanbul, Turkey, October 20-24, 2002.

6. **Plunkett LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 2001.

7. **Plunkett LM .** Differences and Similarities Between Children and Adults in their Exposure and Response to Environmental Chemicals: An Update Since 1992. Invited Speaker at ToxForum, Aspen CO, July 2001.

8. **Plunkett LM.** Do current FIFRA guideline tests protect infants and children? Lead as a case study. Invited speaker at the Sixteenth International Neurotoxicology Conference, Pesticides and Susceptible Populations: Who is at Risk and When? Little Rock, Arkansas, September 13-16 1998

9. **Plunkett LM.** An overview of biotechnology regulations: the USFDA and the USEPA. Lecturer at University of Houston at Clearlake, October 16 1998.

10. Rodricks JV, Santamaria AB, **Plunkett LM.** Risk Assessment as a Tool in Litigation: A Discussion of the Uses and Their Limits [Presented by **Plunkett LM**]. Society for Risk Analysis, , New Orleans, LA. December 10 1996.

11. **Plunkett LM.** Current Issues in Lead Exposure and Risk Assessment. Symposia at the annual meeting of The American College of Toxicology, Valley Forge, PA. November 9 1996.

12. **Plunkett LM .** An Overview of Biotechnology Regulations: Environmental Regulations. Lecturer at the South Texas School of Law, October 1995.

13. **Plunkett LM.** An Overview of Biotechnology Regulations: FDA Regulations. Lecturer at the South Texas School of Law, October 1995.

14. **Plunkett LM .** A Discussion of Toxicokinetics. Featured speaker at a symposium at the Int. Congress of Toxicol., July 5 1995.

15. **Plunkett LM.** Chutes and Ladders: The Hazardous Journey for R&D to Market. Featured speaker at the Futurist's Conference, Irvine, CA, June 28, 1995.

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UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Producst Liability Litigation
MDL DOCKET NO. 1769
This Document Relates to ALL CASES

EXPERT REPORT OF
Laura M. Plunkett, Ph.D., DABT
September 6, 2008

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies, based in Houston, Texas, is a consulting firm that works at the interface of biological science, regulatory affairs and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Before joining Integrative Biostrategies in 2001, I was head of the consulting firm known as Plunkett & Associates.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral

research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. During this time, I studied drugs of all classes that affect brain function, including anti-psychotic drugs. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions. Much of my focus was on drugs that affect brain function, which includes anti-psychotics.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products (relating to both Canadian and American regulations), designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labelling regulations and generally acted as a regulatory affairs staff for small companies

in their early stages of product development. A tool common to all work my work as a consultant would be risk assessment, including many projects where risks and benefits of human therapeutics were at issue. Attached here in Appendix A is a copy of my curriculum vitae.

II. Information Reviewed

7. During the course of work on this case, I have reviewed the following materials:

a) scientific literature relating to the pharmacology and toxicology of anti-psychotic drugs in general and quetiapine (Seroquel) in particular;

b) labelling for Seroquel as provided by the Physician's Desk Reference; and

c) regulations of the U.S. Food and Drug Administration (FDA) relating to the development, approval, labelling and marketing of prescription drug products.

III. Summary of Bipolar Disorder and Schizophrenia

8. Schizophrenia is a major mental illness described by the Diagnostic and Statistical Manual of Mental Disorders ("DSM IV") as a psychotic disorder that is a chronic, severe and disabling brain disease. The hallmark of schizophrenia is disordered thought and perception. Typical symptoms include delusions and hallucinations. While most people diagnosed with schizophrenia are not gainfully employed, a substantial minority do have gainful employment.

9. Bipolar disorder is described by the DSM IV as a mood disorder. Bipolar disorder is a major mental illness, the hallmark of which is manic episodes marked by a euphoric, irritable or expansive mood. Patients with bipolar disorder usually also experience major depressive episodes.

IV. Atypical Anti-psychotics

10. The primary class of drugs used to treat symptoms of schizophrenia and bipolar disorder is known as anti-psychotics. Additionally, mood stabilizers or anti-depressants may also be used to treat bipolar disorder.

11. Anti-psychotics fall into two general categories: the newly developed atypical anti-psychotics and the older, conventional or typical anti-psychotics. The term "atypical" is

applied to the newer drugs mainly because of the lower risks of adverse neurological effects known as extrapyramidal effects. As a general rule, because many atypical anti-psychotics (including Seroquel) still have patent protection, generic versions are not available and as such they are more expensive to purchase and, as a result, more profitable to the manufacturer.

12. Conventional, or typical, anti-psychotics as a group include drugs of a number of different chemical classes. These drugs have efficacy to treat both bipolar disorder and schizophrenia but also often exhibit significant side effects, including risk of acute and long-term neurological side effects, including extrapyramidal effects.

13. Atypical anti-psychotic drugs are considered as having less of a risk of producing extrapyramidal side effects, the unwanted neurological effects that are characterized by changes in movement. In fact, the goal of introducing atypical anti-psychotics to the marketplace was to provide an effective treatment that also improved the quality of life of the patient. While the exact mechanisms responsible for the pharmacological differences between typical and atypical anti-psychotics have not yet been clearly defined, differences have been identified in the pattern of brain neurotransmitter receptor systems affected by the various drugs, effects that can be seen in responses elicited in animal models and/or effects that relate to the pharmacological and toxicological responses in humans.

14. Anti-psychotics will only treat the symptoms of schizophrenia and bipolar disorder; there is no "cure" for such disorders. The etiology of schizophrenia and bipolar disorder also remains to be elucidated, although genetics appears to play some role in these disorders.

15. Quetiapine, marketed in the U.S. under the trade name of Seroquel, is a widely prescribed prescription drug product that was approved by the FDA in 1997 for the treatment of schizophrenia. Seroquel was subsequently approved for management of acute manic episodes associated with bipolar disorder in 2004. I believe that Seroquel is also widely prescribed for off-label uses, including the treatment of sleep disorders, control of agitation, anxiety, aggression and behavioural disturbances.

16. The psychotic symptoms treated with atypical anti-psychotic drugs such as Seroquel include disordered thought processes, disorganized and/or irrational behaviour, and degrees of altered mood, from severe agitation to severe withdrawal. Other drugs that have been or are used in the treatment of psychotic disorders include phenothiazines (*e.g.*, chlorpromazine, also known as Thorazine; thioridazine, also known as Mellaril), thioxanthines (*e.g.*, chloprothixene, also known as Taractan; thiothixene, also known as Navane), haloperidol (Haldol), clozapine (Clorazil), aripiprazole (Abilify), loxapine (Loxitane), molindrone (Moban), pimozide (Orap), olanzapine (Zyprexa), riperidone (Risperdal), and ziprasidone (Geodon). The optimum therapy for treating schizophrenia and bipolar disorder is chosen for each patient based on the patient's medical history, including any risks of known side effects of the drug, and the patient's response to the drug in relation to the drug's efficacy and adverse events.

17. The pharmacology of Seroquel and other similar anti-psychotic drugs is described in many textbooks and review articles (*e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edition.* 2006. Brunton, L.L. et al. (eds.), McGraw-Hill: New York, chapter 18). Seroquel produces its therapeutic and adverse effects through its activity on various receptor systems in the brain and throughout the body. Seroquel is known to be an antagonist of D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, H_1, α_1, and α_2 receptors. The efficacy of Seroquel and other atypical anti-psychotic drugs has been linked to dopaminergic and serotonergic system antagonist activity. However, the exact mechanism by which atypical anti-psychotic drugs produce their effects in schizophrenia and bipolar disorders is not known.

V. Seroquel and Associated Health Risks

18. Seroquel is well absorbed following oral administration, with peak concentrations achieved in the blood within 1.5 hours, and an elimination half-life in the range of 6 hours. It is widely distributed in the body and steady state blood levels are achieved within a few days. Following oral administration, Seroquel is extensively metabolized although the major metabolites are not pharmacologically active.

19. Seroquel use has been associated with deaths that have been attributed to severe liver, kidney, and pancreatic damage. Its adverse effects include, but are not limited to,

ketoacidosis, pancreatitis, diabetes mellitus, weight gain, hyperglycemia, blindness, increased thirst, and hypoglycemia. Other serious injuries associated with Seroquel use include: a potentially fatal condition known as neuroleptic malignant syndrome (NMS); tardive dyskinesia, which can cause potentially irreversible, involuntary movements; and other serious health problems associated with the onset of diabetes including heart disease, blindness, coma, seizures and death. These adverse health effects have been reported following both short-term and longer-term use of Seroquel.

20. Some of the adverse health effects associated with Seroquel use have been attributed to activity of the drug on certain receptor systems in the body. For example, orthostatic hypotension seen in some patients administered Seroquel is thought to be attributed to α_1-adrenergic antagonist activity of the drug while somnolence has been attributed to antagonism of histamine type 1 (H_1) receptors by Seroquel.

21. While Seroquel is similar in basic pharmacological profile to other atypical anti-psychotic drugs, including olanzapine and risperidone, the potency of Seroquel as an antagonist at D_2 and 5-HT_{2A} receptors is less than either olanzapine or risperidone. Differences in potency as an antagonist at certain receptor types may explain some of the differences observed among the various atypical anti-psychotics in terms of both efficacy and toxicity.

22. It has been known for decades that many anti-psychotic drugs have effects to alter metabolism that can lead to weight gain and effects on glucose metabolism (*e.g.*, Baldessarini, R.J. 1980. Drugs and the treatment of psychiatric disorders. In: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 6th edition.* A.G. Gilman et al. (Eds.), chapter 19, MacMillan Publishing Co.: New York). However, it has been recognized more recently (since about 1999) that there appear to be differences among the various anti-psychotic drugs in terms of their propensity for inducing weight gain and changes in glucose metabolism, as well as the onset of diabetes (*e.g.*, Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723; American Diabetes Association et al. 2004. *Diabetes Care* 27:596-601; Allison, D.B. et al. 1999. *Am. J. Psychiatry* 156:1686-1896; Bobes, J. et al. 2003. *Schizophr. Res.* 62:77-88; Wetterling, T. 2001. *Drug Saf.* 24:59-73; Buse, J.B. et al. 2003. *J. Clin. Epidemiol.* 56:164-170). Moreover, it has

now been recognized that clinically significant hyperglycemia and diabetic complications can occur during anti-psychotic treatment both with and without changes in body weight (Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiatry* 59:337-345; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93). Because of the differences apparent among different anti-psychotic agents in terms of risks of diabetes and weight gain, the effects of Seroquel cannot be considered simply a "class" effect for atypical anti-psychotic drugs (Newcomer, J.W. 2005. *CNS Drugs* 19(Suppl. 1):1-93). Different anti-psychotic drugs, including the second generation atypical anti-psychotic agents, have different toxicological profiles.

23. Between January 1997 and July 2002, numerous adverse drug event reports were submitted to the FDA. These reports indicated that patients consuming Seroquel experienced significant adverse health effects, including hyperglycemia, diabetes, exacerbation of pre-existing diabetes, ketoacidosis, and death. These adverse event reports were discussed in an article by Koller *et al.* (2004. *J. Clin. Psychiatry* 65:857-863). The authors concluded that use of Seroiquel may unmask or precipitate hyperglycemia in patients.

24. Case reports linking Seroquel use with hyperglycemia and/or diabetes appeared in the published literature as early as 1999 (*e.g.,* Sobel *et al.* 1999. *J. Clin. Psychiatry* 60:556-557).

25. A large study involving the U.S. Veterans' Administration (Sernyak, M.J. *et al.* 2002. *Am. J. Psychiatry* 159:561-566) was performed in 1999 where records from all patients being treated nationally with anti-psychotics were examined. The authors reported that there was an increased risk of diabetes with exposure to certain anti-psychotic drugs. One of the drugs shown to be associated with an increased risk was Seroquel.

26. At a conference in Europe in 2002, Lambert and colleagues reported the results of a matched case-control study of California Medicaid claims data from 1997 through 2000. They found that there was an increased risk of developing type II diabetes in patients exposed to Seroquel (Lambert *et al.* 2002. *Eur. Neuropsychopharmacol.* 12:S307).

27. In or about August of 2003, a report in the *Wall Street Journal* showed that a study of 19,878 U.S. military veterans between October 1998 and October 2001 indicated that

Seroquel and other members of the new class of anti-psychotic drugs posed a higher risk of diabetes. The article stated that effects were most pronounced with Seroquel.

28. At a conference of the *International Society for Pharmacoepidemiology* held in Philadelphia on August 23 and 24, 2003, study data were reported that showed that patients on Seroquel had 3.34 times as many cases of diabetes as those on older antipsychotic drugs.

29. When considered as a whole in a weight-of-the evidence assessment, the available scientific data indicate that Seroquel can cause physiological effects known to be risk factors for diabetes, including increased body weight and other metabolic effects, and can cause diabetes itself. The scientific data include case reports published on an ongoing basis since 1999 (Sobel, M. et al. 1999. *J. Clin. Psychiatry* 60:556-557; Procshyn, R.M. et al. 2000. *Can. J. Psychiatry* 45:668-669; Wilson, D.R. et al. 2002. *Schizophr. Res.* 59:1-6; Domon, S.E. and C.S. Cargile. 2002. *J. Am. Acad. Child Adolesc. Psychiatry* 41: 495-496; Sneed, K.B. et al. 2003. *J. Am. Board Fam. Pract.* 16:251-254), clinical data (*e.g.*, Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Wirshing, D.A. et al. 2002. *J. Clin. Psychiatry* 63:856-865; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96; the product insert for Seroquel in 2005, *Physician's Desk Reference*, pp. 662-667), a survey of adverse drug reports (Koller, E.A. et al. 2004. *J. Clin. Psychiatry* 65:857-863), epidemiological data assembled since 1999 (Sobel et al. 1999. *J. Clin. Psychiatry* 60:556-557; Sernyak, M.J. et al. 2002. *Am. J. Psychiatry* 159:561-566; Ollendorf, D.A. et al. 2004. *MedGenMed* 6:5; Citrome, L. et al. 2004. *Psychiatr. Serv.* 55:1006-1013; Leslie, D.L. and R.A. Rosenheck. 2004. *Am. J. Psychiatry* 161:1709-1711; Feldman, P.D. et al. 2004. *J. Am. Med. Dir. Assoc.* 5:38-46; Sacchetti, E. et al. 2005. *Int. Clin. Psychopharm.* 20:33-37; Lambert, B.L. et al. 2006. *Am. J. Epidemiol.* 164:672-681; Guo, J.J. et al. 2006. *J. Clin. Psychiatry* 67:1055-1061; Guo, J.J. et al. 2007. *Pharmacotherapy* 27:27-35), and animal data (Cope, M.B. et al. 2005. *Int. J. Obesity* 29:607-614). Each source of information is important in the analysis of the risks associated with

use of Seroquel, and is consistent with accepted methods for establishing causation in a weight-of-the-evidence analysis (Hill, A.B. 1965. *Proc. Royal Soc. Med.* 58:295-300).

30. I believe that the available scientific data demonstrate that Seroquel consumption and use can cause adverse metabolic effects that include, but are not limited to an increased risk of clinically significant body weight gain, hyperglycemia, altered glucose metabolism, and an increased risk of diabetes and diabetes-related complications.

31. It is also important to remember that although clinical trials had been performed with Seroquel as part of the drug development process, such trials are limited in their ability to identify risks associated with drug use by the general population. This is because such drug development clinical trials are performed in either healthy volunteers or in patients that have often been pre-screened for the propensity to develop adverse effects such as hyperglycemia or diabetes, with such patients then usually excluded from studies. It is only after a drug has been placed on the market, and wider exposure is seen, that a true picture of the adverse effects associated with a drug can be observed. As a result, I believe that companies have the duty to carefully monitor their drugs after approval and during marketing for either the existence of new adverse events or a higher than expected incidence of known adverse effects.

32. Scientific studies have established that there are apparent differences among anti-psychotic drugs in terms of risks of diabetes, weight gain and other adverse health effects discussed above. As a result of these differences, and differences in toxicological profiles, I believe that side effects arising through the consumption of Seroquel cannot be described as a "class effect" for all atypical anti-psychotic drugs.

33. Finally, when considering the adverse health effects associated with use of Seroquel, it is important to realize that Seroquel is not unique in terms of its efficacy. Studies have shown that other anti-psychotic drugs have similar effectiveness to Seroquel but have less risk for hyperglycemia, weight gain, metabolic disturbances and diabetes. Therefore, there are safer alternative therapies that could be used that would also provide for effective treatment but with fewer side effects.

34. For example, in the CATIE Schizophrenia Trial, a trial sponsored by the National Institute of Mental Health which is the largest trial conducted to date comparing efficacy and safety of some of the most prescribed anti-psychotic drugs, it was shown that clozapine was more effective than other atypical anti-psychotics (*i.e.*, Seroquel, Zyprexa, Risperdal). Further, when all of the atypical agents studied were examined, including Seroquel, none of the agents was more effective or better tolerated than the typical anti-psychotic, perphenazine (Manschreck, T.C. and R.A. Boshes. 2007. *Harv. Rev. Psychiatry* 15:245-258; Nasrallah, H.A. 2007. *J. Clin. Psychiatry* 68:5-11).

VI. Mechanisms Underlying the Adverse Effects of Seroquel

35. Although the exact molecular mechanisms responsible for the metabolic effects of Seroquel have not been established, there are data that describe the basic mechanisms that lead to the effects of Seroquel on body weight gain and altered glucose metabolism, and eventually diabetes. However, weight gain is not a prerequisite for atypical anti-psychotic drug-induced effects on glucose metabolism and induction of type II diabetes (Newcomer, J.W. 2004. *Clin. Ther.* 26:1936-1946; Newcomer, J.W. 2005. *CNS Drugs* 19(S1):1-93; Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2002. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2001. *Am. J. Med.* 111:716-723; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

36. Clinically significant body weight gain is often seen with administration of Seroquel to patients (Borison, R. et al. 1996. *J. Clin. Psychopharmacol.* 16:158-169; Small, J.G. et al. 1997. *Arch. Gen. Psychiatry* 54:549-557; Arvanitis, L.A. and B.G. Miller. 1997. *Biol. Psychiatry* 42:233-246; Peuskens, J. and C.G. Link. 1997. *Acta Psychiatr, Scand.* 96:265-273; Copolov, D.L. et al. 2000. *Psychol. Med.* 30:95-105; Brecher, M. et al. 2000. *Int. J. Psych. Clin. Pract.* 4:287-291; Nasrallah, H. 2003. *Psychoneuroendocrinology* 28:83-96). The effects of atypical anti-psychotics on weight gain have been shown to be attributable to both increased caloric intake (increased appetite) and decreased energy expenditure (Gothelf, D. et al. 2002. *Am.*

J. Psychiatry 159:1055-1057; Virkkunen, M. et al. 2002. *Pharmacopsychiatry* 35:124-126). These mechanisms for increased body weight gain are consistent with the fact that Seroquel has effects on neurotransmitter systems in the brain that affect appetite and mood. It is well-established in the medical literature that a clinically significant increase in body weight is a risk factor for diabetes (*e.g.*, Foster, D.W. 1994. Diabetes mellitus. In: *Harrison=s Principles of Internal Medicine, 13th edition.* K.J. Isselbacher et al. (Eds.), chapter 337, McGraw-Hill: New York). Therefore, any effect of Seroquel to increase body weight is a significant risk for the development of diabetes.

37. As discussed above, Seroquel administration to patients has been linked to an increased risk of type II diabetes (see the weight of the evidence discussion above). The mechanisms responsible for development of type II diabetes have been examined in both animals and humans. Type II diabetes is a disorder that is characterized by normal or high levels of insulin in blood at the same time that glucose levels in blood are elevated. The condition is sometimes referred to as insulin resistance. Insulin normally acts to promote transport of glucose across cell membranes (reducing blood glucose levels) and to inhibit lipolysis. Resistance to the activity of insulin leads to hyperlipidemia and eventually to hyperglycemia and even development of diabetes. Although increased weight gain has been discussed as a likely factor in the development of insulin resistance and drug-induced diabetes, there are data that demonstrate Seroquel-induced effects on glucose metabolism and insulin resistance that are independent of weight gain.

38. Observational data has shown that atypical anti-psychotics that are structurally similar to Seroquel (*i.e.*, clozapine and olanzapine) can exert direct effects on glucose-insulin homeostasis by induction of hyperinsulinemia (Melkersson, K.I. et al. 2003. *Psychopharmacology* 170:157-166; Melkersson, K.I. et al. 2000. *J. Clin. Psychiatry* 61:742-749). The increased levels of insulin lead to decreased insulin sensitivity in tissues and could lead to an insulin-resistant state (Melkersson, K. and M-L. Dahl. 2004. *Drugs* 64:701-723). *In vitro* data have shown that olanzapine stimulates insulin release from pancreatic islet cells (Melkersson, K. 2004. *Eur. Neuropsychopharmacology* 14:115-119). Regardless of the exact molecular changes that may occur in any one patient treated with Seroquel, these data indicate

that atypical anti-psychotics that are pharmacologically and chemically similar to Seroquel have direct and indirect effects on glucose metabolism that are consistent with the development of insulin resistance, hyperglycemia and potentially type II diabetes. Considered together, the mechanistic data provide evidence for both direct and indirect effects that can lead to disturbances in glucose metabolism and development of type II diabetes. These findings are supported by findings with atypical anti-psychotic drugs, including data specific to Seroquel, that have linked the drugs to induction of diabetes, apart from the induction of weight gain (Dwyer, D.S. and D. Donohoe. 2003. *Pharm. Biochem. Behav.* 75:255-260; Ardizzone, T.D. et al. 2001. *Brain Res.* 923:82-90; Dwyer, D.S. et al. 1999. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* 23:69-80; Newcomer, J.W. et al. 2002. *Arch. Gen. Psychiat.* 59:337-345; Koller, E.A. and P. Murali. 2003. *Pharmacotherapy* 22:841-852; Koller, E. et al. 2004. *J. Clin. Psychiatry* 65:857-863; Ebenbichler, C.F. et al. 2003. *J. Clin. Psychiat.* 64:1436-1439).

39. The data indicate that administration of Seroquel can cause diabetes and/or the effects on glucose metabolism that can lead to diabetes. The data also indicate that Seroquel poses a greater risk for hyperglycemia and diabetes, both with and without body weight gain, than some other anti-psychotic drugs.

40. Although available studies have focused on the association of type II diabetes with Seroquel treatment, as well as treatment with other atypical anti-psychotic drugs, the toxicity of these drugs, which includes altered glucose metabolism, obesity, and hyperglycemia, would also be significant risk factors for individuals with undiagnosed type I diabetes or a genetic predisposition for type I diabetes. Type I diabetes is characterized by a loss of insulin secretion capacity due to the loss of beta cells in the pancreas. The loss of insulin secretion capacity means that type I diabetics would need to rely on exogenous sources of insulin to control blood glucose levels. Therefore, it is only common sense that any effects of a drug such as Seroquel to affect glucose metabolism or blood glucose levels would be a greater risk for individuals who already are at risk of type I diabetes or who are not yet exhibiting clinical signs and symptoms of type I diabetes.

VII. Warning of Health Risks

41. Despite the findings of the studies discussed above, AstraZeneca failed to warn the FDA, physicians, other health practitioners, and patients of the adverse metabolic effects associated with the consumption of Seroquel at the time these risks were first identified.

42. A review of the most recent product labelling for Seroquel that is available to health professionals demonstrates that, in my opinion, the warnings related to risks of hyperglycemia and diabetes in particular are not adequate to convey the risks posed by Seroquel itself. The discussion of hyperglycemia and diabetes is put forth as an effect of anti-psychotics in general only.

43. At the time that the Seroquel labelling failed to adequately warn physicians of the risks associated with use of the drug, other international regulatory bodies were requiring specific changes to product labelling related to the risks of hyperglycemia and diabetes that were associated with Seroquel, not anti-psychotics in general. For example, in Japan, physicians were being specifically warned to not use Seroquel in patients with a history of diabetes and to monitor patients for development of glucose abnormalities during treatment with Seroquel, regardless of their medical history. Additionally, in 2005 permission to market Seroquel in France had been denied due in part to the risk of hyperglycemia and diabetes associated specifically with Seroquel, again not anti-psychotics in general. Accordingly, I believe that the physicians in the U.S., and as a result their patients, were not being supplied with adequate risk information related to hyperglycemia and diabetes even though actions had been taken in other countries to warn physicians and patients of these risks.

44. As a result, I believe that the product warnings were wholly inadequate to warn physicians and their patients of the significant adverse metabolic effects associated with the consumption of Seroquel. Nonetheless, Seroquel was marketed heavily as safe and effective for the treatment of bipolar disorder and schizophrenia, promising fewer side effects than other similar treatments including the other atypical anti-psychotics on the market. Further, Seroquel was being prescribed by physicians for treatment of conditions other than bipolar disorder and schizophrenia (off-label use), which use I believe was known by Astra-Zeneca.

VIII. Conclusion

45. In conclusion, based on my training and experience as a pharmacologist, toxicologist, and risk assessor, it is my opinion that Seroquel can cause hyperglycemia and diabetes. The adverse health effects, including these adverse metabolic effects, associated with the consumption and use of Seroquel were predictable based on the known pharmacological profile of the drug and would have been predicted prior to the approval of Seroquel based on the known effects of other structurally similar anti-psychotic drugs. Moreover, the adverse health effects associated with Seroquel consumption and use can be serious, life-threatening conditions and were recognized in the published medical literature soon after the drug was approved. All opinions expressed in this report are based on a reasonable degree of scientific certainty.

IX. Compensation

46. My compensation by plaintiff's attorney in this matter is at the rate of $300.00 per hour for review of documents and materials related to the case and $400.00 per hour for testimony.

X. Previous Testimony

47. A list of my previous testimony for the past four years is included in Appendix B.

I certify that the foregoing statements made by me are true and correct. Executed this 6th day of September 2008 at Houston, Texas.

LISA GONZALES
MY COMMISSION EXPIRES
February 15, 2009

Laura Plunkett, Ph.D., D.A.B.T.

STATE OF TEXAS)

) ss.

COUNTY OF HARRIS

Subscribed and sworn to me

Before this 6th day of Sept. 2008.

Signature of Notary Public

My Commission Expires February 15, 2009

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT for previous 4 years

Year	Case Name	Law Firm Represented
2004	*Freeman v. Bayer* *Caldwell v. Bayer* *January 6, 2004*	Beckenstein & Oxford (Beaumont, TX)
2004	*Nichols v. Bayer* *January 7, 2004*	Hare, Wynn, Newell, & Newton (Birmingham, AL)
2004	*Sheets v. Perrigo* *February, 2004*	Miller & Associates (Richmond, VA)
2004	*Crowson v. Davol, Inc.* *April 6, 2004*	Hicks Thomas & Lilienstern, LLP (Houston, TX)
2004	*McAllister v. Metabolife* *Deposition - April 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Valverde v. Bayer* *May 26, 2004*	Waters & Kraus (Dallas, TX)
2004	*McAllister v. Metabolife* *Trial - June 15, 2004*	Fibich, Hampton, Garth & Leebron (Houston, TX)
2004	*Havey v. Wyeth* *Deposition – July 16, 2004*	Waters & Kraus (Dallas, TX)
2004	*Jensen v. Wyeth* *Deposition – August 12, 2004*	Neilsen & Senior (Salt Lake City, UT)
2004	*Thompson v. Wyeth* *Deposition – August 24, 2004*	Williams, Dailey, O'Leary, Craine & Love (Portland, Oregon)
2004	*Havey v. Wyeth* *Trial – September 14, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Valverde v. Bayer Corp* *Trial – September 29, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Berg v. Bayer* *Deposition – October 13, 2004*	Williams Love O'Leary Craine & Powers, P.C. (Portland, OR)

Year	Case Name	Law Firm Represented
2004	*Turney v. Novartis Consumer* *Deposition – October 19, 2004*	Waters & Kraus (Dallas, Texas)
2004	*Spencer v. Duramed* *Deposition – November 9, 2004*	Ashcraft & Gerel (Washington, DC)
2005	*Hawkins v. Metabolife* *Deposition – February 1, 2005*	Simmons-Cooper, L.L.C. (East Alton, IL)
2005	*Spears v. Swift* *Deposition – February 8, 2005*	Johanson & Fairless, LLP (Sugar Land, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – March 1, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Turney v. Novartis* *Trial – March 7, 2005*	Waters & Kraus (Dallas, Texas)
2005	*Kelly Longoria, Douglas Woody v. Metabolife Intl.* *Deposition – March 14, 2005*	Blizzard Law Firm (Houston, TX)
2005	*Sandejo-Villa v. Rexall Sundown, Inc., et al* *Deposition – April 19, 2005*	Snapka, Turman & Waterhouse (Corpus Christi, TX)
2005	*Vogt v. Wyeth* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Crowe v. Perrigo* *Deposition – May 18, 2005*	Ashcraft & Gerel (Washington, DC)
2005	*Moore v. Wyeth* *Deposition – August 17, 2005*	Abraham Watkins Sorrel & Friend (Houston, TX)
2005	*Sheets v. Perrigo* *Deposition – September 12, 2005*	Miller & Associates (Richmond, VA)
2005	*Blanton* *Deposition – November 11, 2005*	Owens & Fazio (Dallas, TX)
2006	*Geers v. Wyeth* *Trial Testimony – January 23, 2006*	Fleming & Associates (Houston, TX)

Year	Case Name	Law Firm Represented
2006	*Smoot v. AST Sports Science, Inc. et. al.* *Deposition– April 26, 2006*	Ashcraft & Gerel (Alexandria, VA)
2006	*Arrigale/Grossberg v. Merck* *Deposition - June 1, 2006*	Robinson, Calcagnie, & Robinson (California)
2006	*Anderson v. Merck* *Deposition – June 5, 2006*	Abraham Watkins (Houston, TX)
2006	*McNeill v. Ford* *Trial Testimony – June 15, 2006*	Fleming & Associates (Houston, TX)
2006	*Miller v. Merck* *Deposition – June 20, 2006*	Abraham Watkins (Houston, TX)
2006	*Rhone-Poulenc* *Deposition – October 4, 2006*	White and Williams, LLP (Philadelphia, PA)
2007	*Allen* *Deposition – January 25, 2007*	Blizzard Law Firm (Houston, TX)
2007	*Arts Street Fire* *Deposition – February 6, 2007*	The Caluda Law Firm (Metairie, LA)
2007	*Zyprexa MDL 1596* *Deposition – April 25, 2007*	Fibich, Hampton & Leebron (Houston, TX)
2007	*Armendariz* *Deposition – June 13, 2007*	Waters & Kraus (Dallas, TX)
2007	*NJ Education Day* *Testimony – July 24, 2007*	Weitz & Luxembourg (New York, NY)
2008	*Arts Street Fire* *Deposition – February 27, 2008*	The Caluda Law Firm (Metairie, LA)
2008	*Steele v. GSK* *Deposition – July 10, 2008*	Tracey Law Firm (Houston, TX)

EXHIBIT 45

C

Effective:[See Text Amendments] to June 29, 2006

Code of Federal Regulations
Title 21. Food and Drugs
Chapter I. Food and Drug Administration, Department of Health and Human Services
Subchapter C. Drugs: General
Part 201. Labeling
Subpart B. Labeling Requirements for Prescription Drugs and/or Insulin

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

<Text of section effective until June 30, 2006.>

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

(a) Description.

(1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for la- bels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) Clinical Pharmacology.

(1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of informa- tion.

(2) Data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this section of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.126(b) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.126(b) of this chapter.

(c) Indications and Usage.

(1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(d) Contraindications. Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and

Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) Precautions. Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General. This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other specific section or subsection of the labeling.

(2) Information for patients. This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information or Medication Guide required under this chapter to be distributed to the patient shall be referred to under the "Precautions" section of the labeling and the full text of such patient information or Medication Guide shall be reprinted at the end of the labeling. The print size requirements for the Medication Guide set forth in § 208.20 of this chapter, however, do not apply to the Medication Guide that is reprinted in the professional labeling.

(3) Laboratory tests. This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) Drug interactions. This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions. This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility. This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogen-

ic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) Pregnancy. This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) Teratogenic effects. Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) Pregnancy category A. If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) Pregnancy category B. If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) Pregnancy category C. If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy

Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) Pregnancy category D. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the labeling states: "(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(e) Pregnancy category X. If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) Nonteratogenic effects. Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery. If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers.

(i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systemically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from (name of drug)(or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when (name of drug) is administered to a nursing woman."

(iii) If a drug is absorbed systemically and information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from (name of drug)(or, "Because of the potential for tumorigenicity shown for (name of drug) in (animal or human) studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when (name of drug) is administered to a nursing woman."

(9) Pediatric use.

(i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized

in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (drug name) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (___) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of

the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

(10) Geriatric use.

(i) A specific geriatric indication, if any, that is supported by adequate and well-controlled studies in the geriatric population shall be described under the "Indications and Usage" section of the labeling, and appropriate geriatric dosage shall be stated under the "Dosage and Administration" section of the labeling. The "Geriatric use" subsection shall cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, and other information related to the safe and effective use of the drug in the geriatric population. Unless otherwise noted, information contained in the "Geriatric use" subsection of the labeling shall pertain to use of the drug in persons 65 years of age and older. Data summarized in this subsection of the labeling shall be discussed in more detail, if appropriate, under "Clinical Pharmacology" or the "Clinical Studies" section. As appropriate, this information shall also be contained in "Contraindications," "Warnings," and elsewhere in "Precautions."

(ii) Specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, shall be contained in the "Geriatric use" subsection and shall reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biological license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection shall contain the following statement(s) or reasonable alternative, as applicable, taking into account available information:

(A) If clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

(B) If clinical studies (including studies that are part of marketing applications and other relevant studies available to the sponsor that have not been submitted in the sponsor's applications) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection shall contain the following statement:

Of the total number of subjects in clinical studies of (name of drug), ___ percent were 65 and over, while ___ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

(C) If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling shall contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, shall refer to more detailed discussions in the "Contraindications," "Warnings," "Dosage and Administration," or other sections of the labeling.

(iii)(A) If specific pharmacokinetic or pharmacodynamic studies have been carried out in the elderly, they shall be described briefly in the "Geriatric use" subsection of the labeling and in detail under the "Clinical Pharmacology" section. The "Clinical Pharmacology" section and "Drug interactions" subsection of the "Precautions" section ordinarily contain information on drug-disease and drug-drug interactions that is particularly relevant to the elderly, who are more likely to have concomitant illness and to utilize concomitant drugs.

(B) If a drug is known to be substantially excreted by the kidney, the "Geriatric use" subsection shall include the statement:

"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal func- tion."

(iv) If use of the drug in the elderly appears to cause a specific hazard, the hazard shall be described in the "Geriatric use" subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications," "Warnings," or "Precautions" section of the labeling, and the "Geriatric use" subsection shall refer to those sections.

(v) Labeling under paragraphs (f)(10)(i) through (f)(10)(iii) of this section may include statements, if they would be useful in enhancing safe use of the drug, that reflect good clinical practice or past experience in a particular situation, e.g., for a sedating drug, it could be stated that:

"Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of (name of drug) and observed closely."

(vi) If the sponsor believes that none of the requirements described in paragraphs (f)(10)(i) through (f)(10)(v) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose an alternative statement. FDA may permit omission of the statements if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling. FDA may permit use of an alternative statement if the agency determines that such statement is accurate and appropriate.

(g) Adverse Reactions. An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to (name of drug) is (are)(list reactions). This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are (list reactions), which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are (list reactions)." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.126(b) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(b) of this chapter.

(h) Drug Abuse and Dependence. Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse. This subsection of the labeling shall be based primarily on human data and human experience,

but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence. This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) Overdosage. Under this section heading, the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) Dosage and Administration. This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug

incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) How Supplied. This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) Animal Pharmacology and/or Animal Toxicology. In most cases, the labeling need not include this section. Significant animal data necessary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References". These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.126(b) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

[44 FR 37462, June 26, 1979; 55 FR 11576, March 29, 1990; 59 FR 64249, Dec. 13, 1994; 62 FR 45325, Aug. 27, 1997; 63 FR 66396, Dec. 1, 1998]

SOURCE: 40 FR 13998, March 27, 1975; 51 FR 8182, March 7, 1986; 51 FR 43904, Dec. 5, 1986; 52 FR 2111,

Jan. 20, 1987; 53 FR 4135, Feb. 12, 1988; 54 FR 39635, Sept. 27, 1989, 57 FR 54300, Nov. 18, 1992; 58 FR 45201, Aug. 26, 1993; 62 FR 51515, Oct. 1, 1997; 63 FR 26698, May 13, 1998; 64 FR 400, Jan. 5, 1999, unless otherwise noted.

AUTHORITY: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

LAW REVIEWSA state of extinction: Does Food and Drug Administration approval of a prescription drug label extinguish state claims for inadequate warning? 58 Food & Drug L.J. 287 (2003)."Dot.com medicine"--Labeling in an internet age. 56 Food & Drug L.J. 143 (2001).Is it worth the trouble? The new policy on dissemination of information on off-label drug use under the Food and Drug Administration Modernization Act of 1997. 54 Food & Drug L.J. 645 (1999).Off-label use, prescription, and marketing of FDA-approved drugs: An assessment of legislative and regulatory policy. 51 Fla. L. Rev. 181 (1999).State statutes affecting the labeling of OTC drugs: Constitutionality based on Commerce Clause and federal preemption theories. 46 Food Drug Cosm. L.J. 629 (1991).The learned intermediary doctrine: The correct prescription for drug labeling. 48 Rutgers L. Rev. 821 (1996).The mass marketing of prescription drugs and its effect on the learned intermediary doctrine. 25 Okla. City U. L. Rev. 745 (2000).UNITED STATES CODE ANNOTATEDMisbranded drugs and devices, see21 USCA § 352.21 C. F. R. § 201.57, 21 CFR § 201.57

END OF DOCUMENT

EXHIBIT 46

IN THE UNITED STATES DISTRICT COURT

FOR THE MIDDLE DISTRICT OF FLORIDA

ORLANDO DIVISION

MDL DOCKET NUMBER: 1769

IN RE: SEROQUEL PRODUCTS LIABILITY LITIGATION

DEPOSITION OF:

DONNA K. ARNETT, M.S.P.H

VOLUME II

**** HIGHLY CONFIDENTIAL ****

S T I P U L A T I O N S

IT IS STIPULATED AND AGREED, by and between the parties through their respective counsel, that the deposition of:

DONNA ARNETT, M.S.P.H.

may be taken before Lisa Bailey, Notary Public, State at Large, at University of Alabama at Birmingham, 1655 University Boulevard, Birmingham, Alabama, on October 7, 2008 commencing at approximately 8:30 a.m.

in Table A2 when you look at diabetes and you look at quetiapine and placebo? And you can use the calculator.

A. So you want the relative risk?

Q. Yes.

A. Can I borrow your pen? The relative risk, also known as the risk ratio, is 2.02.

Q. If you look at page 10 of your report, the top paragraph, you see the FDA analyzed all of Study 126 and 127. Your conclusion at the bottom says, "Not unexpectedly given these differences in glucose and insulin resistance, the risk for diabetes was 2.02"?

A. Yes.

Q. And the source for that is that table, isn't it, Doctor? And by "that table," the table we just marked and you just analyzed, Exhibit 24.

A. Yes.

Q. Now, that's not a relative risk that's based on incidence density, is it?

A. No. It's the number of events.

Q. If you look at incidence density instead of number of events, what is the relative risk when you look at quetiapine versus placebo in Table A2? Did you calculate it, Doctor?

A. I'm still trying to understand where the numbers from this table -- what they actually mean when they say "density."

Q. When you calculate the relative risk in Table A2 of diabetes melitis and you look at incidence density, .4 for quetiapine and .6 for placebo, what is the relative risk, Doctor?

A. For -- this does not make sense to me as an epidemiologist. The rate ratio is almost identical to the incidence -- cumulative incidence ratio. But the incidence density ratio is .46 divided by -- .4 divided by .6.

Q. And what is that?

A Point --

MR. BLIZZARD: Are you just asking for the mathematical calculation?

A. -- 67.

Q. Doctor, the relative risk, if you look at incidence density in Table A2 for diabetes melitis when you look at quetiapine versus placebo, .4 to .6 is a relative risk of .67, correct?

A. Yes.

Q. Now --

A. But it's unusual -- I've never seen in all of my 25 years of epidemiologic experience a

rate ratio and an incidence density ratio come on opposite sides of 1. So there's something I don't understand about their calculation of density. So I can't say with accuracy that that's a correct ratio.

Q. You can't say with accuracy that it's not either --

A. No.

Q. -- because you haven't analyzed it, right?

A. I'd have to see how these are calculated. It's fishy.

Q. The opinion that you gave yesterday that Seroquel is unsafe, do you remember that?

A. Yes.

Q. Your opinion that Seroquel is unsafe, is that -- withdrawn.

Is it your opinion that the chemical composition of Seroquel is defective?

A. I cannot comment with expertise about the chemical composition.

Q. Is there a safer alternative design for Seroquel that you think AstraZeneca should have used?

A. From the totality of the data with

respect to weight and metabolic abnormalities, we've discussed the comparator drug Haloperidol appeared safer with those indices. So I can't comment on what AstraZeneca should have created or in contrast to Seroquel. But there are other alternatives out there that are metabolically safer.

Q. Is it your opinion that, according to you, because Seroquel has a greater weight of -- risk of weight and metabolic abnormalities compared to Haloperidol, that, therefore, Seroquel is unsafe?

A. In the absence of having -- let me rephrase that.

In light of the fact that there were other drugs without those metabolic abnormalities that could be used to treat psychoses, in that respect, Seroquel was unsafe.

Q. You haven't looked at any of the first-generation antipsychotics or second-generation antipsychotics to evaluate them for the risk of metabolic abnormalities, have you, Doctor?

A. With respect to the --

MR. BLIZZARD: Object to the form.

A. -- studies that I've evaluated, yes.

Q. Doctor, I asked you whether or not you've evaluated the risk of -- well, let's stick with Haloperidol, for example.

Do you know for Haloperidol how that compares to Seroquel with respect to the risk of EPS?

A. In the follow-up study from the CATIE trial, it appears to be equivalent.

Q. Is it your testimony that involved Haldol?

A. No.

Q. Let me go back to my original question. Is there a safer alternative design for Seroquel that you claim AstraZeneca should have used?

A. I don't -- I don't have an answer.

Q. Did the vast majority of patients who used Seroquel benefit from it?

A. Could you be more specific by the term "vast"?

Q. Did the majority of the patients who used Seroquel benefit from the medicine, ma'am?

MR. BLIZZARD: Object to the form.

A. In my opinion, no. Because there were such high dropout rates in all of the clinical trials that I reviewed that it would indicate that

the vast majority had no benefit because they dropped out.

Q. Do you know how many patients have used Seroquel since it's been brought to the market in the U.S.?

A. No.

Q. Any idea what percentage of patients who used it think it benefited and helped them?

A. It's irrelevant in the aspect of the question at hand regarding diabetes and metabolic risk. Because in randomized clinical trials where you're using a placebo control, you can evaluate benefit versus harm better than observational studies post marketing.

Q. The FDA had all the information, Doctor, to evaluate the risk of metabolic effects from Seroquel when it approved Seroquel, did it not?

A. I could not find all of the metabolic risks that was in the FDA, so I can't answer for the FDA. I couldn't find it.

Q. Did the FDA conclude that the benefits of Seroquel outweighed the risks when the drug was brought to market?

A. I'll make the assumption that they did. I haven't reviewed their documentation.

Q. Has the FDA repeatedly approved Seroquel as safe and effective and that the benefits outweigh the risks --

MR. BLIZZARD: Object to the form.

Q. -- since it's been brought on the market?

A. As I indicated earlier in my testimony, I haven't extensively evaluated all of the FDA documents with respect to Seroquel.

Q. Do you know that Seroquel has been approved for multiple indications since it's been brought to the market in the United States?

MR. BLIZZARD: Object to the form.

A. Yes.

Q. And on each of those occasions, the FDA concluded the benefits outweighed the risks, correct?

MR. BLIZZARD: Object to the form.

A. I can't define what the FDA decided.

Q. You don't know what it means when the FDA approves a medicine for an indication?

A. Yes.

Q. What does it mean?

A. I'm making an assumption that it means that -- actually, I'm not going to make any

assumptions.

Q. So you don't know?

A. I want to go and review their actual criteria before I answer that question.

Q. As you sit here today, you don't know what it means when the FDA approves a medicine for an indication?

A. All I can do as a scientist is -- am I bothering you by the way I'm answering your question?

Q. No. I'm asking do you know --

A. You're just sighing and rolling your eyes at me.

Q. Doctor, I'm just asking you if you know. You're answering and giving very long-winded answers. And my question is very specific.

MR. BLIZZARD: No, no, no. She was giving an answer. Now you've used the opportunity where she was asking you to please stop rolling your eyes to formulate some new question because you didn't like the answer she was about to give. She's doing a very good job of trying to be responsive to you.

BY MR. GOLDMAN:

Q. Doctor, I'm only rolling my eyes because

EXHIBIT 47

08-I-99343 sh

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE: Seroquel Products Liability Litigation
MDL DOCKET NO. 1769

This document relates to all Group One Trial Cases:

Janice Burns v. AstraZeneca LP, et al. Case No. 6:07-cv-15959
Sandra Carter v. AstraZeneca LP, et al. Case No. 6:07-cv-13234
Connie Curley v. AstraZeneca LP, et al. Case No. 6:07-cv-15701
Linda Guinn v. AstraZeneca LP, et al. Case No. 6:07-cv-10291
David Haller v. AstraZeneca LP, et al. Case No. 6:07-cv-15733
Hope Lorditch v. AstraZeneca LP, et al. Case No. 6:07-cv-12657
Eileen McAlexander v. AstraZeneca LP, et al. Case No. 6:07-cv-10360
Clemmie Middleton v. AstraZeneca LP, et al. Case No. 6:07-cv-10949
Charles Ray v. AstraZeneca LP, et al. Case No. 6:07-cv-11102
William Sarmiento v. AstraZeneca LP, et al. Case No. 6:07-cv-10425
Richard Unger v. AstraZeneca LP, et al. Case No. 6:07-cv-15812
Linda Whittington v. AstraZeneca LP, et al. Case No. 6:07-cv-10475

****

ORAL DEPOSITION OF

LAURA M. PLUNKETT, Ph.D., DABT

October 2, 2008

Volume 1

****

looked at some of the Clozapine data because they were head-to-head data. I also looked at -- now, you're talking about just first generation?

Q. Yeah.

A. Oh, okay. Then haloperidol was the main drug, and then there are a few trials that looked at perphenazine.

Q. Okay. Do you think haloperidol is an effective medication in treating mental illness?

A. Yes.

Q. Would you agree with me that first-generation antipsychotic drugs, as a group, are associated with certain movement disorders?

A. Some of them, yes. And some are worse than others, but, yes. In fact, that's how -- if you read my report, I try to start out with sort of a primer on pharmacology. And Goodman & Gilman teaches that there are -- the reasons the second-generations were developed was to try to improve on that safety profile.

Q. So --

MR. ALLEN: Hold on. Take a little break.

(Recess from 12:26 p.m. to 12:27 p.m.)

Q. (BY MR. BROWN) The -- so, as a group, second-generations were studied and ultimately marketed because they had better side effect profiles with respect to movement disorders, correct?

A. I don't know they were ultimately marketed. But that was one of the impetus, looking for drugs that had less of a propensity to produce some of these movement disorders. But what was interesting is if you look at the labeling for the drugs, that statement is not allowed to be put into the labeling. In other words, I don't believe that the evidence has shown head to head, at least to the sufficiency of the FDA, that any one drug has a specific percent advantage over another.

I would agree with you as a class, in general, when you look at first generation versus second, that as a general rule, you expect the second-generations to have less propensity, but that doesn't mean they have no propensity.

Q. Let me ask this question: Have you -- do you have an opinion with respect to whether haloperidol has a better EPS profile than Seroquel?

A. I haven't formed that opinion. I believe that haloperidol has a propensity to produce it and I believe Seroquel does as well.

Q. In doing a risk-benefit analysis, you have to consider side effects, correct?

A. Yes.

Q. Wouldn't you need to know whether one caused EPS more frequently than the other to actually make that assessment?

A. It depends. If you're doing -- it depends what

you're doing with the risk-benefit assessment. My issue -- and maybe this will help you: When I did the risk-benefit assessment here for Seroquel, I was looking for what were the general -- what were the types of risks that had been associated routinely with Seroquel and what were the benefits that were shown? And then when I'm looking at that drug, I make an assessment based upon whether I think the risks outweigh the benefits.

Now, I'm not saying that the risks outweigh the benefits for this drug such that it should be removed from the market. That's not what I'm saying. I'm saying that when I -- and if you look at what my statement is, I believe there are safer alternatives. I believe that if you look at Seroquel, it should not be a first-line agent necessarily because the metabolic risks of this drug are different from some of the other drugs, and that is above and beyond the neuromuscular risks.

That's not to say that there isn't a patient that Seroquel could be given to safely, and it's possible that it is, but I don't think it should be a first-line treatment.

Q. So, it must be so, based on what you just told me, that you have an understanding of the side effect profile of first-generation antipsychotics, correct?

A. Yes.

Q. And you've researched it in forming your opinions

here today, correct?

A. Yes. In general terms, yes.

Q. And do any of the materials you have brought to the dep today or identified in your report discuss the side effect profiles of first-generation antipsychotics?

A. Many of the published articles talk about that. My textbook talks about that. And then you also even have head-to-head clinical data on Seroquel versus some of these other first-generations that talk about side effect profile. So, absolutely, yes.

Q. And you mentioned that there are safer alternatives to Seroquel, correct?

A. I believe there are, yes.

Q. And what are the safer alternatives to Seroquel?

A. I believe that haloperidol would be a safer alternative to Seroquel. I believe that ziprasidone would be a safer alternative to Seroquel, and possibly -- I can't think of the generic name, but Abilify.

Q. And have you carefully reviewed the side effect profiles for haloperidol?

A. I have reviewed the -- I don't know what you mean by "carefully." I certainly, for my perspective in forming my opinions, have reviewed the side effect profile for haloperidol. And in addition to that -- I'm basing my opinions in part on some of the head-to-head studies that I've provided

here for you in my literature and on those disks.

Q. Okay. Do you know what head-to-head studies you looked at that compared haloperidol to Seroquel?

A. I'd have to go through my pile to tell you. I mean, there -- but it's certainly ones -- some of them are cited in my report and then there's others that are on the PDF files that I've given you. But they wouldn't necessarily be cited as a head-to-head study. I'm just telling you that there are studies that -- I know some of the ones in there have haloperidol versus -- usually versus quetiapine and something else as well.

Q. Does haloperidol cause diabetes?

A. I believe that haloperidol has been shown to have some patients that have shown up with metabolic effects certainly because it can produce some weight gain and some of those things. However, I have not formed an opinion in the same way as I have with Seroquel. I have formed the opinion that I think that Seroquel, Zyprexa, and Risperdal -- and I've been very clear on this in my presentation in the New Jersey Education Day -- appear to have a greater and unique risk over a drug like haloperidol and even over, like, ziprasidone and some of the other second-generation drugs.

Q. Did some of the epi literature you rely on quantify the increased risk of diabetes with haloperidol?

A. I'm sure they did because that was a comparative drug

in some of the epi literature.

Q. Would you agree with me that there are a number of studies that show the risk of diabetes is greater for haloperidol versus Seroquel?

A. I'd have to look at the individual studies to answer that, so I don't want to agree with you or disagree with you. If you want to talk about specific numbers like that, I would want to pull the studies out. And if you want to --

Q. We'll do it today.

A. -- show me one, we can look at it.

Q. Would that surprise you? Based on your opinion, would that surprise you that haloperidol had a greater risk, at least in some epi studies, than Seroquel?

A. Not necessarily surprise me. I'd have to look at the individual study though to interpret the data.

Q. And ziprasidone and Abilify are the other two products you think are safer alternatives?

A. I think they could be. Again, it's a patient-specific decision. But I think that based upon the profile I see, they could be safer alternatives.

Q. And as a non-medical doctor, you're never asked for a particular patient what the best medication is, correct?

A. I'm answering this as a pharmacologist. So, if you ask me as a pharmacologist, based upon the information I see, that's how I answer the question, right. I'm not a physician,

so I don't -- I would not make that decision for an individual patient.

Q. Would you agree with me that all drugs have some risk?

A. Yes. I would say that that's a common -- common thing for anything I can think of. Even water has a risk.

Q. So, no drug's a hundred percent safe, correct?

A. That's right.

Q. All drugs have some level of side effects to varying degrees?

A. Yes, some levels, and they differ in severity and occurrence rates.

Q. Medical doctors consider the risks of a medication when they prescribe it, correct?

A. I assume they do and I would hope they do, and I certainly taught my medical students in pharmacology that they should do that.

Q. So, a medical doctor in his or her office today here in Houston, if they're making a determination about what medication's appropriate -- Seroquel, haloperidol, ziprasidone -- they should be doing -- looking at the side effects and the possible benefits and making a determination based on that with that particular patient?

A. Well, again, I think you'd have to ask a doctor what they do. But I certainly would expect my doctor to be familiar

with the side effect profile, as well as the efficacy profile, for any drug that he was to prescribe or attempt to prescribe for me.

Q. Would you agree with me based on your review of all this literature that mentally ill patients are difficult to treat?

A. What do you mean by "difficult to treat"?

Q. That often doctors -- would you agree with me that doctors often need to try a number of different medications in the schizophrenic population -- let's talk about those folks for one minute -- before they can find one that will work?

A. I'm, again, not a physician. I can only speak from what I have read. And certainly from what I have read, I see that doctors often switch patients from one to another. In other words, there's a discontinuation. Doesn't work, you try a different drug, yeah.

Q. Okay. Turn to Paragraph 16 in your report.

A. 16?

Q. Yeah.

MR. ALLEN: Okay. I didn't understand you. Did you say --

MR. LASKER: 16.

MR. ALLEN: 16? I thought -- I thought somebody said "60." I didn't remember there being that many.

Q. (BY MR. BROWN) Dr. Plunkett, I wanted to look at

EXHIBIT 5

IN THE UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

IN RE:

SEROQUEL PRODUCTS LIABILTY LITIGATION

CASE NO. 6:06-md-01769-ACC-DAB

MDL DOCKET NO. 1769

April 24, 2008

CONFIDENTIAL Videotaped Oral Deposition of KEVIN GEOFFREY BIRKETT, held in the offices of Golkow Technologies, Inc., One Liberty Place, 51st Floor, Philadelphia, Pennsylvania beginning at approximately 9:00 a.m., before Ann V. Kaufmann, a Registered Professional Reporter, Certified Realtime Reporter, Approved Reporter of the U.S. District Court, and a Notary Public.

GOLKOW TECHNOLOGIES, INC.
One Liberty Place, 51st Floor
Philadelphia, Pennsylvania 19103
877.370.3377

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A. It was more based on market experience than testing.
Q. Okay. And then as part of marketing do you also get involved in delivering the message?
A. We in the global function would deliver the global strategy, which would lay out the key claims that we felt were most important to the brand. We'd also lay out the long-term plan for the brand. The local messages in the U.S., China, Japan, U.K. would be done by the local operating company.
Q. Okay. So you guys were involved with the overall strategy for developing the message, testing the message, and then you would provide it to the local companies in the U.S. or wherever to deliver the message; right?
A. We were really testing the product, suggesting the optimal message. And then how the product was promoted locally varied upon local market circumstances and the label in

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that country.
Q. Okay. But there were core messages that the company developed; right?
A. Yes. But whether they could be used in absolute and every marketing company was very rare, for various different reasons.
Q. Okay. But there was a core message group, wasn't there?
A. There wasn't a group called the core message group.
Q. No, I'm sorry, I wasn't making myself clear. There were core messages that the company developed; right?
A. Yes.
Q. For Seroquel?
A. Yes.
Q. Okay. And then there were core -- there was actually a core detailing set of slides that was available as well; correct?
A. I don't think that's a good

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terminology and it's not what I'm familiar with. There was a core set of messages that we were recommending the marketing companies would use if the clinical trials delivered the data to support them. There was no global detail aid. Detail aids are very prescriptified and used in one country. I think it's not valid to have a global detail aid.
(Below-described document marked Birkett Exhibit 2.)
BY MR. BLIZZARD:
Q. I'm going to show you what I'm going to mark as Exhibit No. 2. And I will hand one to your counsel.
MR. AUSTIN: Thank you.
Q. Could you tell me what this is?
A. This is an item called a sales story flow. It's not a detail aid. This is a means to say to the marketing companies that as the clinical results of our product unroll, we would

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like this to form the basis of our arguments that we use when promoting Seroquel in different markets around the world.
Q. Okay. If you turn over to the Page 3, which is the first page that contains details about the -- what this document is, do you see what it says there?
A. Yeah, a core detail flow.
Q. Okay. So this is to be used with -- in detailing, isn't it?
A. No. There's a difference between a detail flow and a detail aid. This is to give people a guide. A detail aid is a document that's used in practice.
This document was never printed and never used in a marketing company. This was to guide people in marketing companies. The detail aid would be a glossy printed item that would be used to promote to doctors.
Q. Okay. Now I see what

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distinction you are making. You are saying that this was the document that originated from your group that went out to all the marketing companies that proposed a flow of detailing when salespeople actually went into doctors' offices?

A. No. This was designed to give to the marketing people in the different markets to say to them that this could be a good detail flow to use if the data supports it, if your local label supports it. But the ultimate decision of what would be promoted country by country and in some instances would mirror this and in some instances would be completely different.

Q. Hold on a second. Who prepared this?

A. A global brand manager.

Q. And who was that?

A. Alison Wilke.

Q. And did she work for you?

A. She worked for somebody who

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worked for me, the global brand director.

Q. Okay. So she was under your direction; right?

A. Yes.

Q. And actually if you look at this document, doesn't this document say -- give proposed things to say to doctors to deliver messages to doctors about Seroquel based upon data that this Alison Wilke is saying is available and it supports these claims?

A. Yes; but every time this was reviewed by an individual marketing company, it would be reviewed by their clinical and regulatory team. And they would say this may or may not work in America, France, China, or Germany. They had to take global responsibility based on their local data.

Q. Okay. You are not trying to avoid responsibility for this, are you?

A. No, no. I think these

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documents are a very good guide, but they should never be used by a marketing company without it being rigorously approved by all of their local team.

Q. Okay. Well, did you guys look at this rigorously?

A. This was looked at rigorously by the commercial team and the clinical team.

Q. Okay. Within your group?

A. The clinical team wasn't in my group. That's a separate group.

Q. Okay. Did they provide support for your group?

A. Yes.

Q. Okay. So with the support of the clinical group, this was examined rigorously; correct?

A. Yes.

Q. And then sent out to the marketing companies throughout the world who were also supposed to look at it rigorously; correct?

A. Let me check, because the

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problem with this form is I don't even know if this ever went to the marketing companies. So from this, what you have shown me here, this may have been a draft document. It looks like it was. And so I don't even know that this went to the marketing companies.

Q. Do you know it didn't?

A. I don't know it did.

Q. Well, do you know it didn't?

A. No, I don't know it didn't.

Q. Okay. Well, let's look at some of the things that are said here. If you look at the first page, where it says "The following pages represent a core detail flow and backup data" --

MR. AUSTIN: I'm assuming you mean Page 1?

MR. BLIZZARD: No. I actually mean the third page, which is the page that has the substance of -- where the substance of the document begins.

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analysts.
Q. Well, you are correct about that, but it's not limited to pharmaceuticals, is it?
A. Certainly not. But it's limited to the financial analyst community; they are the people who generally are interested in Reuters.
Q. Yeah. Do you know what its reach is?
A. I don't know.
Q. Do you know what "reach" is?
A. I do.
Q. And what does it mean?
A. It means the number of people that you can reach through a specific medium.
Q. Okay. Is it an international or worldwide service?
A. Reuters is international.
Q. Okay. It says in the first paragraph: "I called our friend at Reuters - he was very personable but

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equally probing - more so than usual." So he was asking some tough questions?
A. Yes.
Q. Okay. It says: "I didn't give any hard facts but said the following after an intense battering of questions - I stuck to my 'script.'"
A. Yes.
Q. So you had a script for this interview?
A. No. But what we tended to do was that we had regular meetings with the people in our corporate headquarters at Stanhope Gate. We gave them the key points of note on any product because they like to be appraised of latest developments. I just used the script that we gave them so that I knew that I wasn't going to go anywhere that the company didn't want me to go.
Q. Okay. And that's generally what you did when you talked to reporters; correct?
A. Yes. The issue with

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talking to reporters, as I'm sure you are aware, they can be, as I point out here, extraordinarily probing and they can take some of the things that you tell them out of context. So I was trying to be extremely careful.
Q. Okay. Look over on the second page. It says: "He finished (sic) on why Zyprexa was doing so badly" -- do you see that paragraph?
A. Yes.
Q. -- "and asked if it was weight - I said weight - eps and a number of issues where we had superior offering." Do you see that?
A. Yeah. And that's absolutely correct.
Q. Well, did you -- you had an opportunity to tell him about the EPS findings that you had recently learned about with respect to your own product; right?
A. But the issue is we wouldn't be comparing apples with apples

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if I did that.
Q. Nonetheless, you had an opportunity within a month of finding out about these EPS findings to get the word out about what the findings were; right?
A. It would not have been appropriate. It would not have shown a good balance of data across the overall database for Seroquel to make that conclusion at that time. That's why the team were running extra studies.
So what I was saying here very clearly was in the treatment of schizophrenia and mania, which are the labeled indications for Zyprexa and Seroquel, because Zyprexa has much more EPS and much more severe weight gain, that's why we're winning and they're losing, which was factually correct.
Q. Well, I guess -- was telling them about Seroquel's EPS findings on the script?
A. I don't know how the script

Page 330

currently reads; but up until we decided to do another study from BOLDER, we always said that Seroquel in the treatment of schizophrenia and mania had a unique EPS tolerability profile, which it did, and I believe it still does.

Q. That was actually the cornerstone of the marketing strategy for Seroquel, wasn't it?

A. There was actually three points to the promotion.

Q. What were they besides superior on EPS?

A. Unsurpassed efficacy, superior EPS to all other agents and similar to placebo, and negligible prolactin and sexual side effects --

Q. Okay.

A. -- which were unique.

Q. And those three claims were the cornerstone of the Seroquel marketing strategy; correct?

A. Yes.

Q. Okay. Now I'm going to

Page 331

hand you what I'm going to mark as Exhibit No. 29 to your deposition.

A. Thank you.

(Below-described document marked Birkett Exhibit 29.)

BY MR. BLIZZARD:

Q. After you received these surprise -- is it fair to say that these findings on EPS in the BOLDER study came as a surprise to you?

A. I was surprised. I wasn't shocked. And we'd always postulated that when you indicate a product for a new series of disease targets, you'll have a different efficacy and side effect profile. So to have an EPS profile similar to placebo was an extraordinary thing. And we weren't arrogant enough to think that if we indicated Seroquel in all these different diseases, that would always remain.

Q. Right.

A. So surprise; not shocked.

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Q. Okay. And that's another reason why you don't want to promote for off-label use, correct, because the side effect profile might be different in a different population? Right?

A. That's why we never promoted off label.

Q. Okay. Because that could cause patient safety issues, couldn't it?

A. If doctors decide to use a product off label, it's outside the reach of the data sheet and our purview, and that's why we never promoted off label.

Q. Okay. And whether you are promoting it off label, educating people about it off label, or encouraging off-label use, you can run into some surprise side effect profiles if you have it used outside the label; right?

A. Any product if used by a clinician outside its label in a specific country could give results that

Page 333

are a surprise to the clinician and the company.

Q. Okay. Now, when you received these surprise findings about EPS coming out of BOLDER, did you take a look at some of the other studies that had previously been done to determine whether they were consistent or inconsistent?

A. No. But I remember that the head of our clinical team at the time asked for that analysis, which I applauded as a very good thing to do.

Q. Okay. And who was that?

A. Bob Holland.

Q. Okay. now, if you look at the last e-mail on the first page of this exhibit, do you see that this is written by a -- by Martin -- actually by Didier -- how do you pronounce that last name?

A. I think it's Didier Meulien. I'm sort of --

Q. French?

Page 557

have sworn under oath -- it's going to be on the record and the jury is going to see it -- that the marketing department was consulted on the core data sheet, and my only question is what was the consultations on the core data sheet involving Seroquel? What was the marketing department's role in that consultation?

MR. AUSTIN: Object to form.

A. To be aware of the discussions and the clinical and scientific rationale around why the data sheet may change.

Q. Why did you need to know that?

A. Because ultimately when the data sheet changed, we would have the responsibility to promote the product.

Q. And so, therefore, your promotion and what you may say or may not say could be affected by the core data sheet; right?

A. The core messages that we

Page 558

would try and deliver for any product of course had to be in line with the core data sheet; but the core data sheet was the ultimate document and it was a technically derived document.

Q. So if hyperglycemia and diabetes were added to the core data sheet, it could affect your role in marketing about what you could say and couldn't say about the product; correct?

A. Not necessarily. I think it's very important to just remind everybody that the key rationale and benefit for Seroquel in all my times in AstraZeneca was unsurpassed efficacy, excellent tolerability on EPS, and excellent tolerability on prolactin.

MR. ALLEN: We're going to take a break right now. But when we come back, I want to remind you of that "unsurpassed efficacy." We're going to pick that up after the break.

THE WITNESS: All right.

MR. ALLEN: All right.

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Thank you, sir.

THE WITNESS: Thank you.

THE VIDEOGRAPHER: It's 25 minutes after 10 o'clock. Going off the record.

(Recess.)

THE VIDEOGRAPHER: It's 39 minutes after 10 o'clock. It is Tape 2. We're back on the record.

BY MR. ALLEN:

Q. Ready to proceed?

A. Yes, thank you.

Q. "Unsurpassed efficacy," that's another one of your exaggerations, isn't it?

MR. AUSTIN: Object to form.

A. No, it's not an exaggeration. It was our way of explaining that Seroquel showed excellent efficacy versus older and newer agents.

Q. But that wasn't true, though, was it?

A. Seroquel at the correct

Page 560

dose shows excellent efficacy, and our belief is that in the correct target patients it is unsurpassed.

Q "Unsurpassed," what does "unsurpassed" mean? I think I know what it means but I want to make sure you and I are communicating.

A. It means in the correct patient treated for the correct indication at the correct dose Seroquel is highly effective and there's nothing more effective.

Q. Nothing more effective?

A. In the right indication at the right dose.

Q. And the right indication would be what?

A. It depends, because now for Seroquel we're lucky enough to have many indications.

Q. Oh, okay. Well, let me talk about -- let's just take schizophrenia first. Does dose have unsurpassed efficacy in schizophrenia?

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A. Seroquel in schizophrenia has a completely unique profile.
Q. Sir, I asked you does it have unsurpassed efficacy.
A. At the correct dose Seroquel is highly effective for the treatment of schizophrenia.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I didn't ask you that. You made the point to Mr. Blizzard yesterday and to me right before the break, and I told you I was going to come back to it, that Seroquel had unsurpassed efficacy. And I'm asking you under oath, does Seroquel have unsurpassed efficacy in the treatment of schizophrenia?
A. At the correct dose in the correct patients, yes, it does.
Q. And when did you have that opinion?
A. My opinion was formulated

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after speaking to all our scientists and after the research program and the regulatory program.
Q. So sometime in the '90s?
A. I first formed the view that Seroquel was an effective and safe product in the '90s, correct.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'm not going to let you change my question, sir. When did you form the opinion that Seroquel had unsurpassed efficacy? When was that?
MR. AUSTIN: Object to form.
A. I can't remember when our global product team decided that that was how we were going to characterize Seroquel's effectiveness. I cannot remember; I'm sorry.
Q. "How we're going to characterize." So, as you've already told us, you did use, "you" being your company, use the characterization of

Page 563

unsurpassed efficacy in your marketing efforts, did you not?
A. Yes, we did.
Q. Thank you, sir. Do you have anything else -- I'm sorry. Do you have anything else you want to say about that?
A. All of our marketing efforts were based on the labels in the individual countries where the product was marketed, and all of the claims we made were absolutely in line with the local core data sheets.
Q. But isn't it a fact the data didn't really look good concerning that issue? And, in fact, the data didn't look good at all and your product, Seroquel, did not even have unsurpassed efficacy over first-generation Haldol; isn't that right?
A. No. At the correct dose in the correct patients Seroquel is highly effective for the treatment of schizophrenia.

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MR. ALLEN: I got one, I got one here, but I need one without; okay?
Q. Sir, I'm trying to get a highlighter. This highlighter ended up with ink on the end so so when you highlight turns black, so I apologize. It will probably happen again.
Do you know that your company, AstraZeneca, did an analysis of the studies done on Seroquel in -- as of around March of 2000 and determined that in fact the data didn't look good and Seroquel didn't have as much efficacy as even Haldol? Did you know that?
A. I know you are looking at a report and you are asking me a question, and I don't remember a specific report that made the conclusion that you are referring to.
Q. Did you ever -- were you ever told by any individuals -- and I'm paraphrasing, but I'm paraphrasing pretty accurately -- concerning the claim of efficacy greater than Haldol in

Page 573

highlighting it for you.
A. Yes, I've got you.
Q. Those are Bates stamps. That's some lawyer term; I have never known what it meant. I guess Mr. Bates invented the stamping system. But that's called a Bates number; okay?
A. Thank you. I've been wondering what it was.
Q. And all I know is we call it that. I don't know anything else. But that's a Bates number.
A. Okay.
Q. I would like you to turn to Bates number page, last two digits, 89; okay? And it is under the heading "Proportion of responders." And, again, I'm not going to read that to you today. We will look at it later. But I want you then to turn the page --
A. I'm sorry. Do you want me to read this or not? I'm sorry.
Q. No, sir.
A. Okay.

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Q. I just wanted to orient you and the jury where we are. "Proportion of responders."
A. Okay.
Q. We turn the page to Page 90 and it is Table 1.
A. Yeah.
Q. Do you see that? And then in very plain English it says: "The following table is an attempt to simplify the claims that could be obtained from these results. A check is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or...last value carried forward." That's LVCF. "An X marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel." Do you see that?
A. I do, thank you.
Q. So a check is where Seroquel wins and an X is where the

Page 575

comparator wins. Do you see that?
A. I do.
Q. Comparators are listed under Table 1 and we have Placebo, Haloperidol. That's Haldol, is it not?
A. It is.
Q. Chlorpromazine, do you know what that is, ?Clozaril?
A. That's not Clozaril.
Q. What is that? Tell me what that is; I'm sorry.
A. It has a whole different series of names depending on which country it exists.
Q. Okay. What is chlorpromazine? Do you know what that is?
A. It has got so many different trade names that it's generally used by the generic.
Q. You are right. And I forgot. So that's an antipsychotic, is it not?
A. Yes. It's a 50-year-old

Page 576

antipsychotic.
Q. That's right. And you are right and I was mistaken. It is a first-generation antipsychotic; correct?
A. Yes, it was one of the first ones.
Q. Yes, sir. You are right. I apologize. We have Risperidone, which is Risperdal, and then other typicals. Do you see that?
A. I do.
Q. A check is where Seroquel wins and, guess what, Seroquel beat a placebo; right?
A. Yes.
Q. And an X is where the comparator wins. On Haldol we have three Xs, do we not?
A. Just, if you wouldn't mind, if I could just study the table.
Q. Yes, sir.
A. Yes, it says here that in this analysis haloperidol scores higher on BPRS, Factor V, and Hostility.

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Q. Yeah. Where did Seroquel score better?
A. It's hard to tell from this analysis, and I don't like the way it's presented, so --
MR. ALLEN: Sir, I object as nonresponsive.
BY MR. ALLEN:
Q. Quite frankly, it is not important whether you like it. Your company wrote this document. "A check is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with" a high dose and "be it using observed cases or...last value carried forward."
I'm asking you, in the comparator to Haldol, where did Seroquel win, according to Table 1?
A. From this table, from a document that's eight years old that I never saw that was never signed, I cannot see where Seroquel is seen as more effective than haloperidol.

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Q. And then chlorpromazine -- I think I'm pronouncing that right -- chlorpromazine, where did Seroquelwin?
A. It looks like -- in fact, I can't tell from this analysis what results were gleaned for Seroquel versus chlorpromazine.
Q. You don't see any checks or any Xs; right?
A. No, I don't.
Q. That's good. So, at least according to the table, Seroquel never won. You don't have any checks; right?
A. I've already said that I don't know whether this is an official document. It's eight years old. I've never seen it. And this could be the view of one person. It might have no widespread statistical validity. You are asking me to guess based on a document I've never seen if Seroquel on this data --
Q. Go ahead.
A. -- is less or more

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effective than chlorpromazine when it's not even marked in the document.
Q. By the way, Dr. Wayne Macfadden was U.S. medical director for Seroquel, was he not?
A. I don't know what his title was.
Q. You know who he is?
A. I think I met him once.
Q. He would have far more knowledge about the clinical studies than you, wouldn't he?
A. Because he was in the clinical function, he'd probably have more intimate knowledge of the studies, correct.
Q. Let's go down to Risperdal. Tell me, according to Table 1, where Seroquel beat Risperdal.
A. It looks like on this analysis in this paper it seems to suggest that risperidone has more efficacy on these measures.
Q. Thank you, sir. Other

Page 580

typicals, where did -- in this analysis in Table 1, where did Seroquel win?
A. You know, I'm not being difficult, but I really don't see the point in answering the question because I don't even know what other typicals are. I think it's a total waste of time having that conversation. It could be anything.
Q. Okay. Well, sir, I just don't, and we will let somebody else determine whether it's a total waste of time.
A. So do you know what those products are?
Q. Yes, sir, I actually do. I'm just saying --
A. Could you tell me and then that might help me?
Q. When you get to take my deposition, I will tell you whatever you want me to tell you.
A. Okay.
Q. I'm saying, according to

Page 601

to -- by the way, if you turn to the first page, it gives you the source of the data, and it's a meta-analysis that was conducted at AstraZeneca. It gives you the design of the trials. And then if we turn back to the conclusions on Page -- Bates Page 07, the last two numbers 07, do you see that? What do you -- right there. Do you see that, 07? They have a conclusion, do they not?

A. Yes, they do.

Q. Let me just read the conclusion to the jury and then ask you a question about it. "Conclusions. The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of equivalence is not ruled out." Did I read that correctly?

A. Yes, you did.

Q. Were you ever informed of that Technical Document No. 5 or its conclusions?

Page 602

A. I have told you twice already no.

Q. Okay. Do you think you maybe should have been informed of this information before you went around making claims of unsurpassed efficacy?

MR. AUSTIN: Object to form.

A. No, because I took my guidance from the head of clinical, the disclosure committee, and the SERM group.

By the way, how is equivalence different from unsurpassed?

MR. ALLEN: Objection, nonresponsive.

BY MR. ALLEN:

Q. Do you really think you get to ask me questions? Is that what you think this process involves, that you get to ask me questions and I give you answers?

MR. AUSTIN: Don't argue with him. Just ask questions.

MR. ALLEN: He's arguing with me.

MR. AUSTIN: He is trying to answer your question.

THE WITNESS: I'm trying to answer your question.

BY MR. ALLEN:

Q. Well, let me ask, since you asked me a question, let me ask you a question: "Unsurpassed," "unsurpassed," what does that mean?

A. It means --

Q. Nobody is better; right?

A. It means equivalent.

Q. So if I really -- I'm trying to think of something. If I tell somebody that I went to a track meet and I saw an athlete that has been unsurpassed, I mean he was -- her, let's say her. Her ability to do the broad jump and the high jump and the relays were unsurpassed, and I was just so impressed and I go and tell you it was unsurpassed, you believe that means I'm saying she was equivalent to everybody

Page 603

Page 604

else at the meet?

A. Possibly, yes. That's the correct grammar. Possibly, yes. She was possibly better; she was possibly equivalent.

Q. And if I come home and -- your child, you said, is 5 years old?

A. I have got two.

Q. How old are they? Mine are 22, 20, and 17. How old are yours?

A. 3 and 5.

Q. When your child comes home from school let's say from first grade and says, "Daddy, I" -- well, I don't think first grade. And your child may be smart because you are smart. So let's just go to fifth grade. Go to fifth grade. "Daddy, my grade in my English class was unsurpassed." What are you going to say, "Congratulations. You made the same grade as everybody else"?

MR. AUSTIN: Object to form.

BY MR. ALLEN:

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Q. Is that what you are telling this jury, is "unsurpassed" means the same?
A. Yes, it does, it means the same as or better. That's exactly what it means.
Q. So -- that's exactly what it means. So when AstraZeneca -- I'm glad to know this. This is interesting and I'm glad we're getting this out here. So when AstraZeneca made the claims of unsurpassed efficacy in regard to Seroquel, what they were meaning to say was, "We are just the same as everybody else"; is that right?
MR. AUSTIN: Object to form.
A. No, but I think we were incredibly careful with the use of grammar to depict what the clinical studies showed and concluded.
Q. You were trying to be tricky?
A. No. We were being incredibly precise and using the correct

Page 606

language. Of course, the language varied from country to country and label to label. The global impression from the safety and efficacy review group was our efficacy was unsurpassed.
Q. And you said in order to use that language, using your words, you were being incredibly careful; is that right?
A. No, I didn't. I said "incredibly precise."
Q. "Incredibly precise"; is that right?
A. Yes.
Q. All right. So if somebody understood the term "unsurpassed efficacy" to mean that you were better than others, they were just being incredibly what, dumb?
A. No. We would never make a claim without showing supporting documentation. So, for example, in the U.S., the doctor could read the label, he could read the FDA approval, and he

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could see the total span of facts.
MR. ALLEN: Objection, nonresponsive.
BY MR. ALLEN:
Q. I'm not asking about the label and I'm not talking about the FDA approval. I'm talking about what you've called at various points during this deposition a slogan or a phrase used in regard to Seroquel, and that was unsurpassed efficacy. Are you telling this jury honestly under oath that you were being so incredibly precise in the marketing of Seroquel that "unsurpassed efficacy" really meant that "We were the same as everybody else"? Is that what you're telling this jury?
A. No. I'm saying that we chose that word to explain the fact that in the studies that we had done, our efficacy was unsurpassed when used in the right patients in the right dose in the right population. You can read a document like this without the context

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and it would be easy to be misunderstood about the total conclusion for what we say about Seroquel. That's why we have a SERM process.
Q. What document did you hold up?
A. That was the document you just gave me.
Q. Well, tell the jury what it was. You held it up. I was through with that document but I -- but what was the document you just held up?
A. This was Exhibit No. 48, which was from 2000, which was in -- between some technical people which was never signed, so it may not have been official, and was just one of a gigantic data set for Seroquel.
Q. Yes, sir. That's -- you chose to get back into it. I'll deal with it. 48, "Conclusions. The intended claim of 'superiority versus Haloperidol' is highly unlikely using these data, however a claim of

EXHIBIT
6

content-type:	multipart/related;type="text/html";boundary="----=_chilkat_702_cf5d_ef254423.258a1b05_REL"
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From: Birkett, Geoff

Sent: Tuesday, March 04, 2003 7:44 PM

To: Bierczynski, Vicky B

Subject: FW: Schizo SSF 3.04

Attachments: Schizo SSF 3.04.ppt

pls do neat colour copy for tomorrow

-----Original Message-----

From: Wilkie, Alison M

Sent: Tuesday, March 04, 2003 2:28 PM

To: Birkett, Geoff

Cc: Bierczynski, Vicky B

Subject: Schizo SSF 3.04

Birkett
EXHIBIT NO. 2
AMC 4/24/08

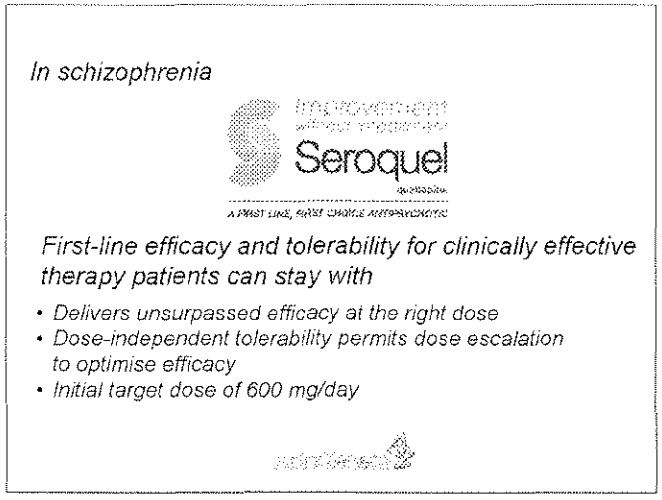
Geoff

Here is the 'tweaked' version for John tomorrow - please let me know if you have any questions.

S339-E00007330.tif

thanks

Alison



The following pages represent a **core detail flow** and **backup data** that support our current position for Seroquel in the treatment of schizophrenia.

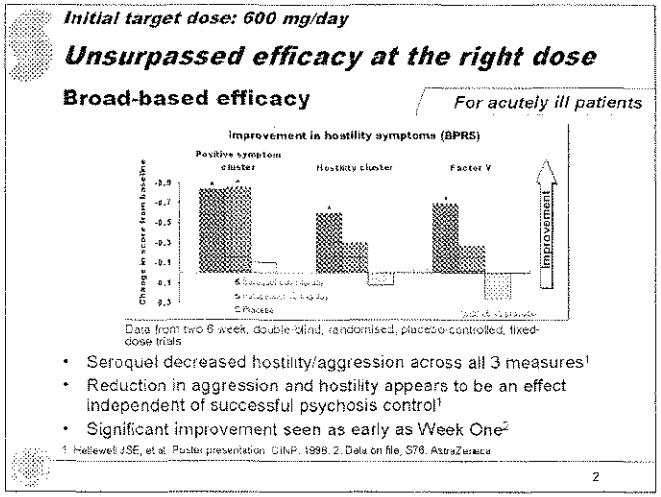
The detail flow

The detail flow presents a succinct summary of the strongest data from our best studies to support Seroquel as the unsurpassed clinical effectiveness at the right dose with:

- Dose-independent tolerability that permits dose escalation to optimise efficacy
- At the right dose—starting with an initial target of 600 mg/day—Seroquel offers unsurpassed clinical effectiveness
- The target 600-mg/day dose is flagged on every page showing efficacy data

Backup data

Backup data are supplied so that local markets can either expand on the data in the core detail or substitute data approved for marketing purposes.



The symptom spectrum for schizophrenia includes aggression and hostility, which need to be controlled without worsening other primary symptoms.

Key communication

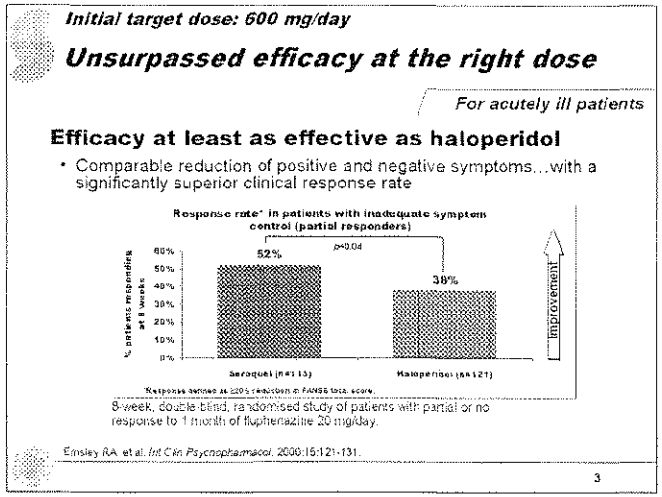
In addition to managing positive and negative symptoms, Seroquel effectively controls aggressive/hostile symptoms.

On this page

- The graph shows Seroquel efficacy in controlling symptoms compared to haloperidol and placebo
- The second bullet notes that, although Seroquel controlled positive and negative symptoms in these studies, improvement in aggression/hostility was an independent effect
- The third bullet emphasises the rapid onset of symptom control

About the study

- Data from two 6-week, well-controlled trials. One trial compared 5 different doses of Seroquel to haloperidol 12 mg/day or placebo. The other trial compared low doses (up to 250 mg/day), and high doses (up to 750 mg/day) to placebo
- Seroquel 600 mg/day was associated with the most consistent improvement
- Seroquel produced greater improvement than haloperidol, but differences were not statistically significant. In addition, changes vs placebo were significant at certain points for Seroquel, but not for haloperidol



Seroquel and haloperidol have been compared in a number of studies. The Emsley study compares these agents in patients with partial treatment failure on other medication.

Key communication

Head to head with haloperidol, Seroquel offers the same—or better—efficacy, and the added advantage of a significantly better clinical response.

On this page

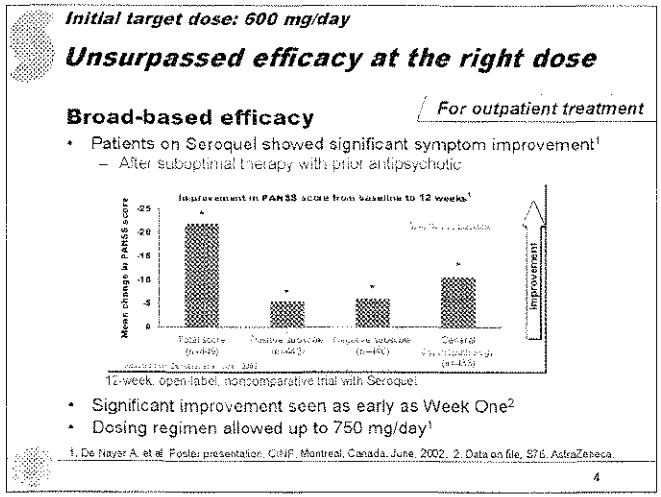
- The graph shows that Seroquel had a significantly better response rate (patients with a ≥20% reduction in PANSS score) than haloperidol
- The bullet highlights the Seroquel advantage—equal efficacy, superior response

About the study

- An 8-week, well-controlled trial of 288 patients who had partial response to typical antipsychotics and no response to fluphenazine
- Seroquel showed marked reduction in PANSS scores greater at Week 8 and Week 12 than haloperidol, although these scores did not reach significance
- More patients taking Seroquel also showed CGI Severity of Illness score ≤3

CGI: Clinical Global Impression. PANSS: Positive and Negative Syndrome Scale.

3



The detail flow starts with efficacy. Seroquel efficacy has been proven in numerous well-controlled clinical trials to control a range of schizophrenia symptoms, including 2 of the most critical kind—positive and negative symptoms.

Key communication

Seroquel significantly improved key symptoms of schizophrenia in patients unsuccessfully treated with another antipsychotic medication

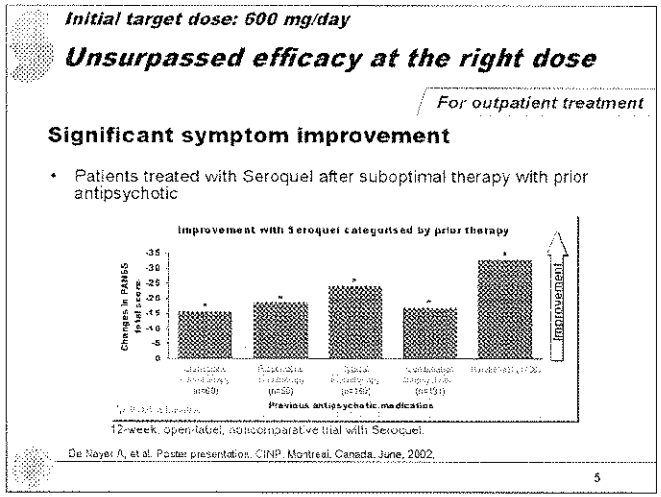
On this page

- This graph shows data from the SPECTRUM study, illustrating the change in PANSS scores for all patients
- *The next page shows improvement categorised by prior suboptimal treatment*
- The second bullet emphasizes rapid onset of improvement—within 1 week
- The third bullet reinforces efficacy at the right dose

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel

PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



The advantages of switching patients to Seroquel from current therapy support its use as a first-line choice.

Key communication

Seroquel improves efficacy, no matter what antipsychotic agent was used prior. So why not start patients on Seroquel, and get the right efficacy from the beginning?

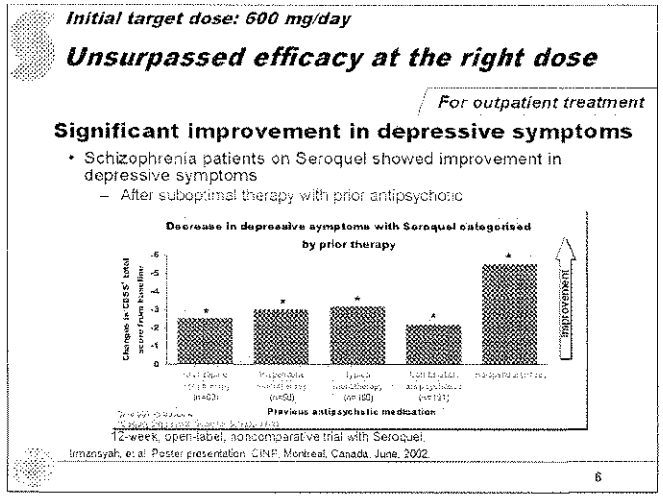
On this page

- This graph demonstrates that, no matter which antipsychotic a patient was switched from, Seroquel provided symptom improvement (as measured by PANSS)

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- Study results show that patients who were started on Seroquel due to partial or no response on previous medication showed symptom improvement and a reduction in EPS side effects
- Similarly, patients who were started on Seroquel because of intolerance to the side effects of their previous medication not only showed a reduction in side-effect incidence, but an improvement in efficacy

EPS: Extrapyramidal symptoms. PANSS: Positive and Negative Syndrome Scale. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



An antipsychotic that can help treat depression, as well as positive, negative, and other symptoms of schizophrenia, is a valuable treatment choice.

Key communication

Improvement with a switch to Seroquel includes reduction in depressive symptoms.

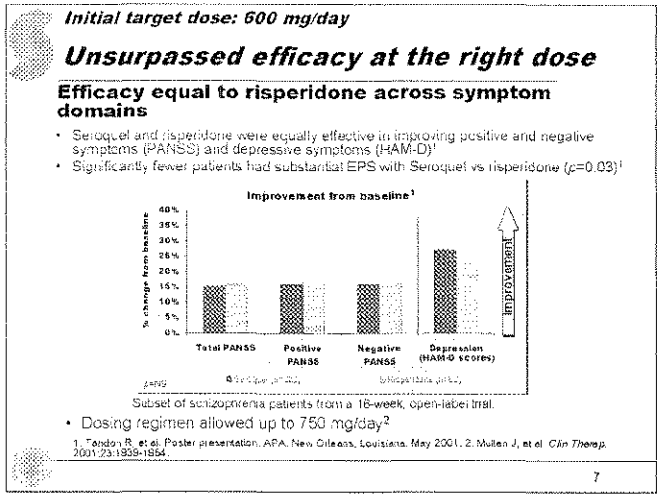
On this page

- This graph demonstrates that, no matter what antipsychotic patients were switched from, Seroquel provided improvement in depressive symptoms

About the study

- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel
- While improvement was seen regardless of whether patients were evaluated as depressed when they started Seroquel, improvement was especially noticeable in patients classified as depressed at baseline

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Data from QUEST compare the symptom relief of Seroquel and risperidone.

Key communication

Seroquel improved positive, negative, and depressive symptoms significantly better than risperidone.

On this page

- The graph, from the QUEST study, shows improvement in PANSS scores and depressive symptoms in a subset of patients with schizophrenia
- The bullet below the graph notes that dosing went as high as 750 mg/day in this study

About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- A subset of patients with schizophrenia was also analysed

HAM-D: Hamilton Rating Scale for Depression. PANSS: Positive and Negative Syndrome Scale.
QUEST: Quetiapine Experience with Safety and Tolerability.

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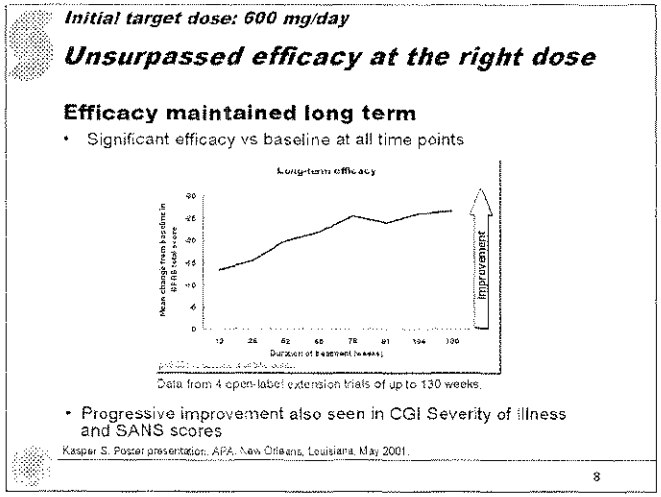


A chronic condition like schizophrenia requires treatment that stays effective long term.

Key communication

Seroquel maintains effective control of symptoms for the long term.

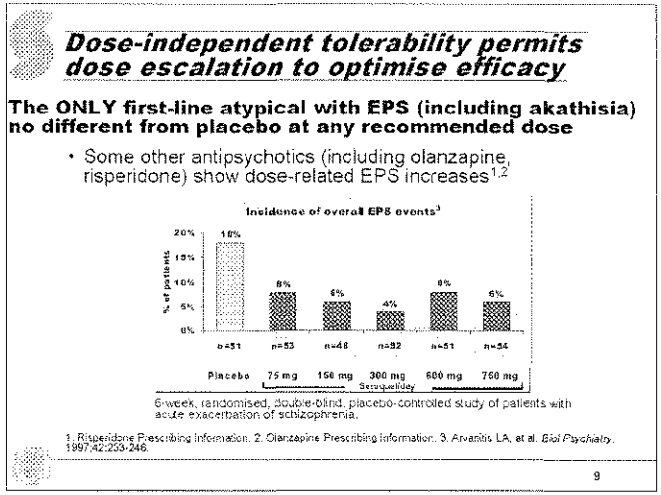
On this page

- The graph plots improvement in total BPRS score (which includes positive and negative symptom measures, as well as 16 other items) over 130 weeks
- The second bullet highlights that, in addition to improving BPRS score, Seroquel therapy improved severity of illness, as measured by CGI, and negative symptoms, as measured by SANS

About the study

- Data analysis for 674 patients in 4 open-label extension trials lasting up to 130 weeks
- Efficacy and tolerability were assessed

BPRS: Brief Psychiatric Rating Scale. SANS: Scale for the Assessment of Negative Symptoms.
CGI: Clinical Global Impression.



After efficacy, the detail flow reinforces the well-known Seroquel safety profile, starting with EPS—a side effect of many antipsychotics that interferes with patients' daily function and compliance. Placebo-level EPS is one of the best-known attributes of Seroquel therapy.

Key communication

Seroquel is the only first-line atypical with EPS no different than placebo at any recommended dose.

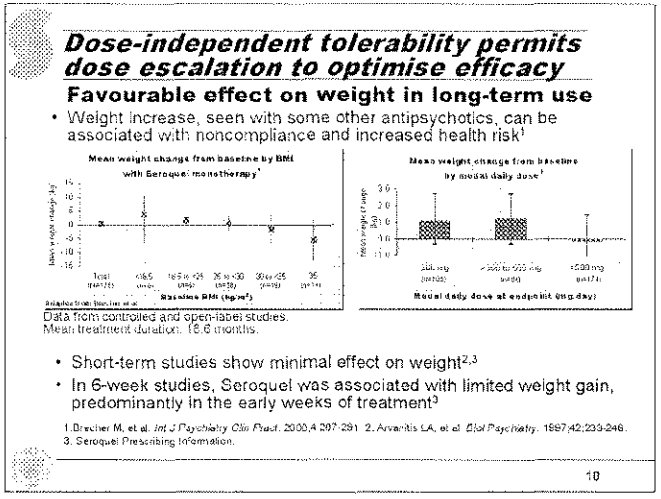
On this page

- The graph shows that incidence of EPS barely changed across Seroquel doses in the study, from the lowest dose (75 mg/day) to the highest dose (750 mg/day)
- The bullet refers to the risperidone and olanzapine PIs, which show increased EPS incidence with increasing doses
- *Other EPS-related data can be found in the backup section*

About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- EPS evaluation was measured by SAS (modified to include akathisia) and AIMS
- Incidence of EPS-reflective events: Seroquel—4-8%, placebo—16%, haloperidol—37%

AIMS: Abnormal Involuntary Movement Scale. EPS: Extrapyramidal symptoms. SAS: Simpson-Angus Scale.



Weight gain is a side effect clearly associated with certain antipsychotics, and can be a primary reason for patient noncompliance.

Key communication

Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain, either in the short or long term or across the recommended dosing range.

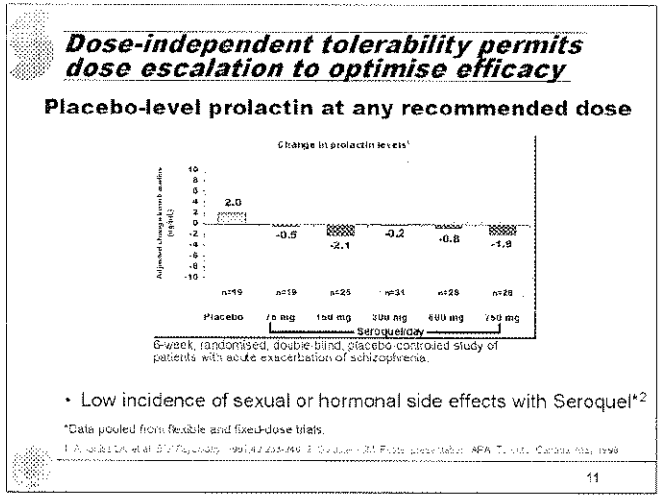
On this page

- The left-hand graph evaluates weight gain over a mean treatment duration of 18 months in patients grouped by baseline BMI category
- The right-hand graph shows weight change categorised by 3 dosing ranges
- Overall, there was almost no mean change in weight. Interestingly, in underweight patients (BMI ≤18), there was beneficial weight gain, while the most overweight groups (BMI 30-35) lost weight

About the study

- Long-term weight-change data for 427 patients were pooled from controlled and uncontrolled studies as well as from their open-label extensions
- In these studies, Seroquel monotherapy was the only antipsychotic treatment allowed

BMI: Body Mass Index.



Abnormal prolactin levels are a common adverse event caused by antipsychotic medication.

Key communication

As with EPS, prolactin levels in patients taking Seroquel are no different than with placebo across the dosing range

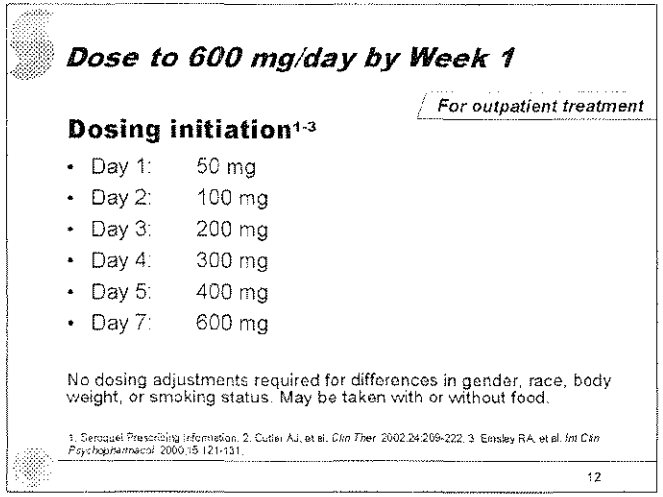
On this page

- The graph shows the minimal change in prolactin levels with Seroquel treatment
- The bullet, from a study by Goldstein, confirms that placebo-level prolactin means minimal risk of sexual or hormonal dysfunction

About the study

- A 6-week, well-controlled study of patients randomised to 1 of 5 fixed doses of Seroquel (n = 255), 12 mg haloperidol (n = 50), or placebo (n = 51)
- In contrast to Seroquel, the difference in prolactin levels between placebo and haloperidol was significant

EPS: Extrapyramidal symptoms.



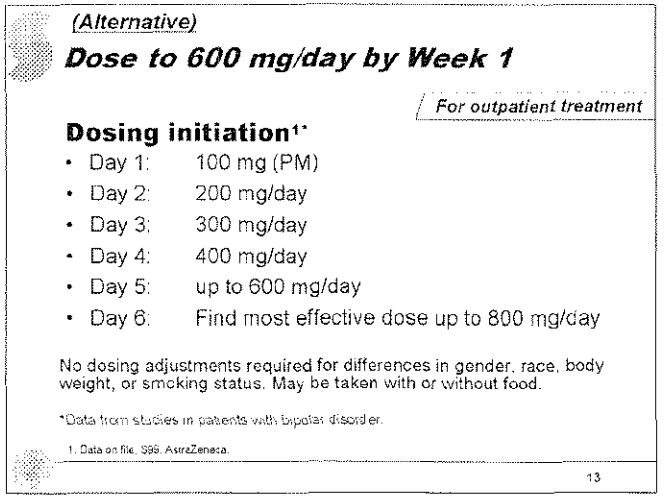
Standard dosing initiation achieves the initial target dose of 600 mg/day by Day 7.

Key communication

Dosing to 600 mg/day is simple and fast.

On this page

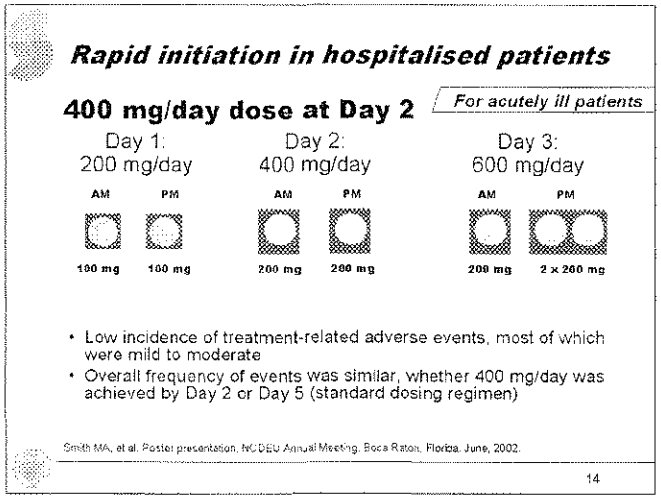
- Physicians are familiar with the dosing schedule from the Prescribing Information for Seroquel



The "four by four" dosing approved for treatment of bipolar mania gets patients to 600 mg/day at Day 5.

Key communication

An accelerated dosing schedule for Seroquel has been proven safe and effective in clinical studies.



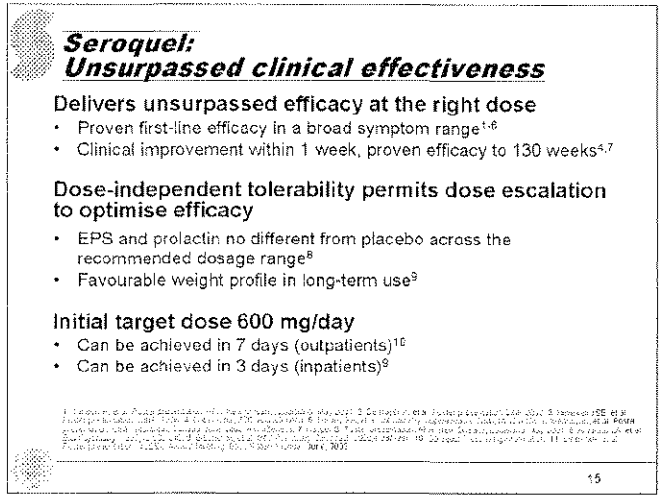
For acutely ill patients, an even more rapid target dose initiation has been shown to have a comparable tolerability profile to traditional dosing schedules.

Key communication

Seroquel can be dosed up to 600 mg/day in fewer than the standard 5 days with safety and tolerability.

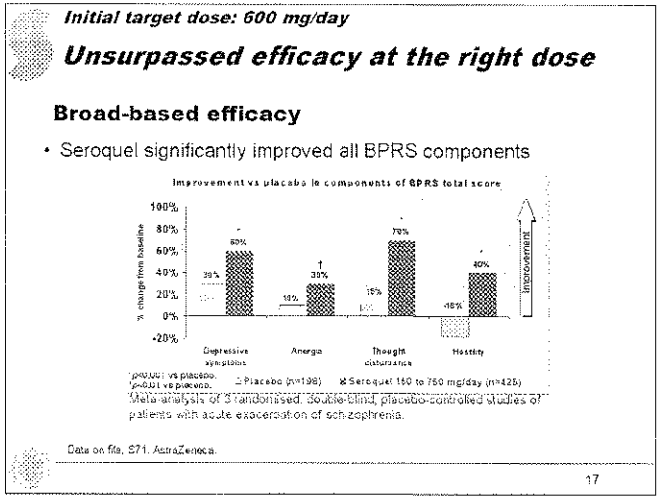
About the study

- This was a 5-day, multicentre, double-blind tolerability/safety study of 69 acutely ill schizophrenia patients randomised to 1 of 3 titration arms
- Patients were dosed to 400 mg/day of Seroquel in 5, 3, or 2 days. Patients were hospitalised during their 2-day washout and 5-day treatment periods
- Frequency of adverse events was similar between the 3 groups. Treatment-related events were few, and most were mild to moderate
- Less than 15% of patients experienced somnolence, with the fewest (8%) in the 2-day titration group
- Laboratory values and vital signs were also similar amongst the treatment arms, including for blood pressure and pulse measurements



This page summarises the key communications in the core detail.

Back-up slides



Additional material on efficacy includes secondary symptoms of schizophrenia.

Key communication

Seroquel effectively manages a wide range of symptoms.

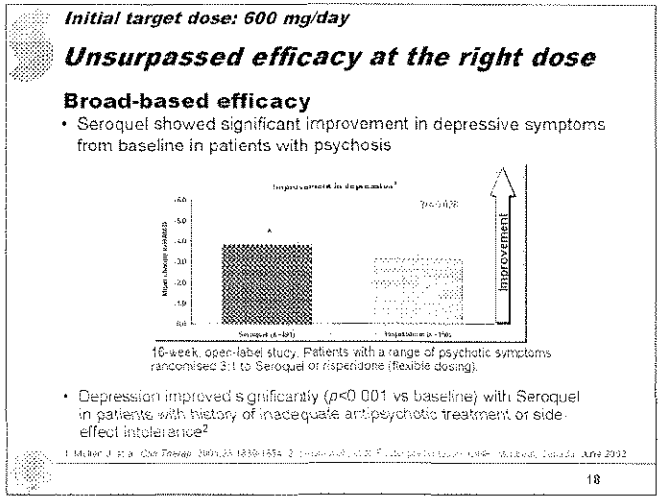
On this page

- Seroquel efficacy in controlling 4 individual symptoms comprising the BPRS, with significant differences vs placebo for each

About the study

- Meta-analysis of three 6-week, well-controlled published studies
- Dosing regimens were different for each study

BPRS: Brief Psychiatric Rating Scale.



Data from QUEST support the proven relief of depression with Seroquel.

Key communication

In patients treated for a range of psychosis symptoms, Seroquel improved depressive symptoms significantly better than risperidone.

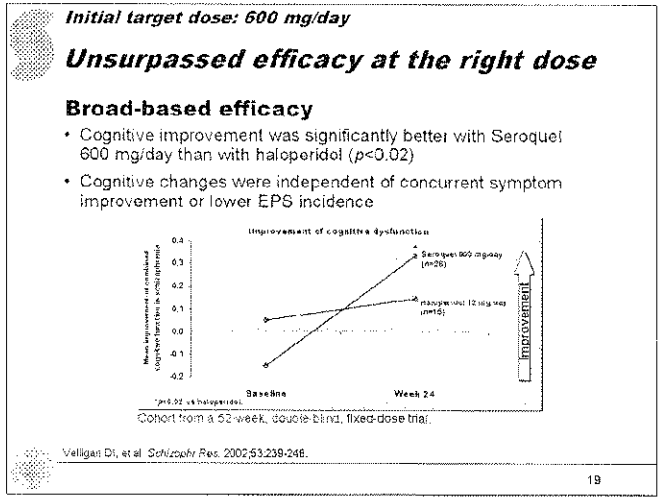
On this page

- The graph, from the QUEST study, shows improvement in depressive symptoms in all patients in the study (ie, all forms of psychosis), measured by change in HAM-D scores
- The bullet below the graph refers to the SPECTRUM study, in which patients with schizophrenia who were unresponsive or intolerant to other antipsychotics were started on Seroquel monotherapy

About the studies

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone
- 641 patients from QUEST were evaluated for depressive symptoms
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were started on Seroquel flexible dosing

HAM-D: Hamilton Rating Scale for Depression. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Improvement in cognitive function can help patients recapture functions critical to basic day-to-day tasks.

Key communication

Seroquel 600 mg/day improved cognitive function significantly better

than haloperidol.

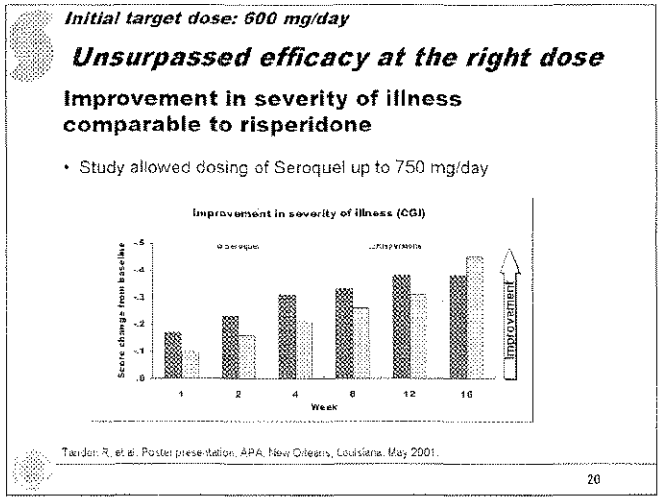
On this page

- The graph and first bullet show the difference between Seroquel and haloperidol in restoring some degree of cognitive function
- The second bullet points out that cognitive improvement was independent of the other benefits of Seroquel (improvement in other symptoms, less incidence of EPS)

About the study

- This was a cohort from a 52-week study of patients on fixed-dose Seroquel, haloperidol, or placebo

EPS: Extrapyramidal symptoms.



Data from QUEST support the efficacy of Seroquel compared to risperidone.

Key communication

Seroquel and risperidone are equally effective in symptom relief.

On this page

- The graph, from the QUEST study, shows global improvement
- The same study showed that Seroquel produced less substantial EPS than risperidone

About the study

- QUEST was a 16-week, open-label study comparing efficacy and tolerability in 751 patients with a range of psychoses treated with Seroquel (flexible dosing) or risperidone

CGI: Clinical Global Improvement. EPS: Extrapyramidal symptoms. QUEST: Quetiapine Experience with Safety and Tolerability. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.

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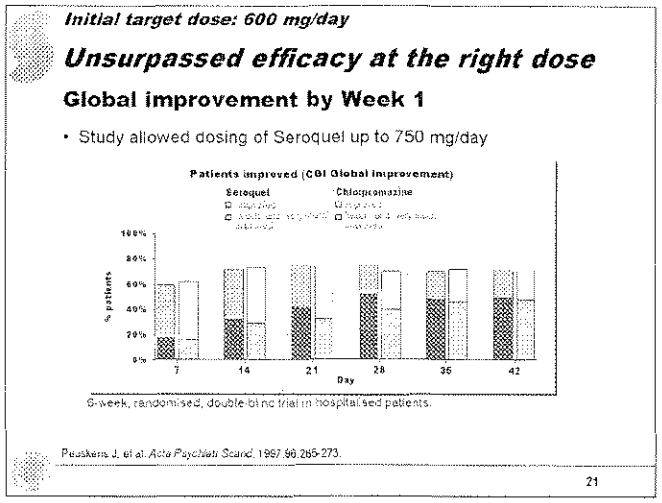


The CGI scale is a well-known, well-accepted measurement of overall symptom improvement.

Key communication

Global improvement—particularly in patients who were "very much" improved—can be seen as early as 1 week and continues to increase throughout treatment.

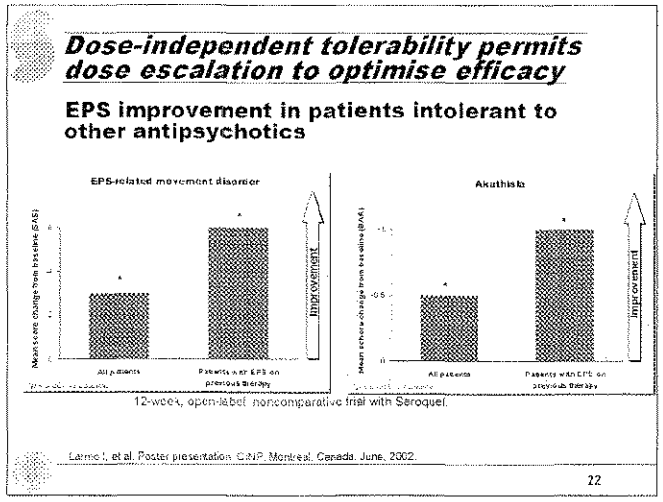
On this page

- The graph shows improvement at Day 7, with the ratio of patients "much" and "very much" improved continuing to grow over the 42 days of the study

About the study

- This was a 6-week study of patients hospitalised with acute exacerbation of schizophrenia
- Tolerability was also evaluated in this study. Fewer patients in the group on Seroquel had parkinsonian symptoms or akathisia vs those in the chlorpromazine group. Elevated prolactin dropped significantly with Seroquel vs chlorpromazine

CGI: Clinical Global Impression



Data from the SPECTRUM study show that a switch to Seroquel can reduce EPS caused by other antipsychotics.

Key communication

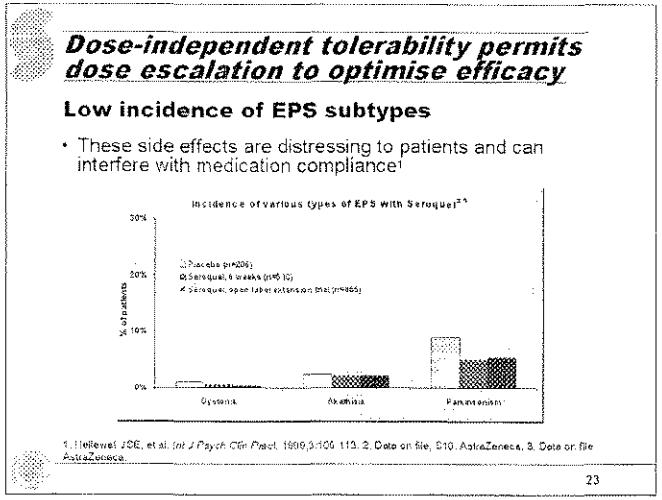
To avoid the EPS caused by other antipsychotics, why not start Seroquel first?

On this page

- The graphs, from the SPECTRUM study, show that the incidence of 2 EPS categories—movement disorder and akathisia—decreased in patients switched to Seroquel from other antipsychotics
- Akathisia is a subset of EPS of particular concern to physicians

- **About the study**
- SPECTRUM was a 12-week, open-label, noncomparative trial in which 509 patients who failed treatment on or were intolerant to other antipsychotics were switched to Seroquel
- A total of 506 patients were evaluated for safety
- EPS was measured by the SAS (movement disorders) and BAS (akathisia) scales

EPS: Extrapyramidal symptoms. SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



More support for placebo-level EPS, by subtype.

Key communication

Seroquel shows no more incidence of EPS than placebo when symptoms are broken down by subtype.

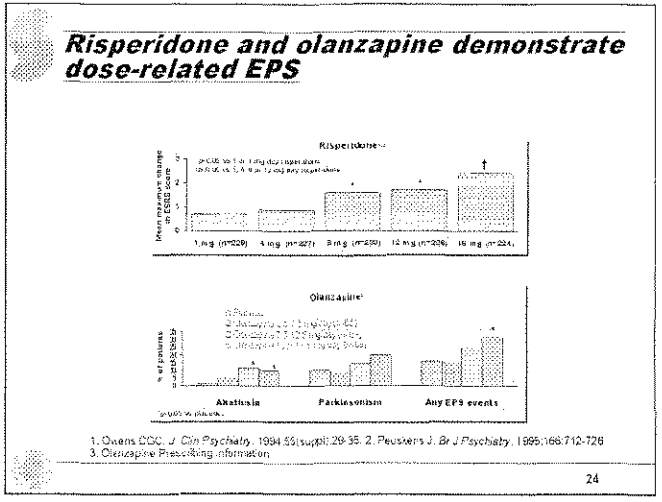
On this page

- 2 studies confirm the Seroquel safety profile

About the studies

- Data on File S10 showed that Seroquel showed no difference vs placebo in EPS subtypes across a 75-mg to 150-mg dosing range
- (Second DOF info to come from client)

EPS: Extrapyramidal symptoms.



EPS data for risperidone and olanzapine confirm the difference in safety profiles between these atypicals and Seroquel.

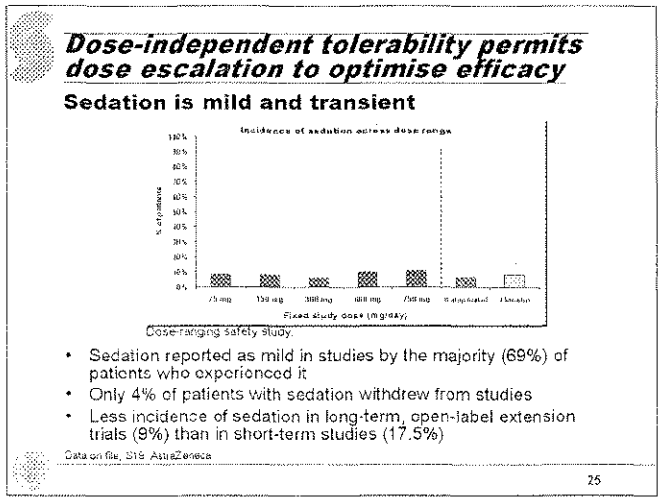
Key communication

Unlike Seroquel, both risperidone and olanzapine show dose-related increases in EPS.

On this page

- These graphs expand on the points made in the core detail piece and backup

EPS: Extrapyramidal symptoms.



Reports of the impact of sedation with Seroquel are greatly exaggerated.

Key communication

Sedation associated with Seroquel therapy is transient and mild across the dosing range

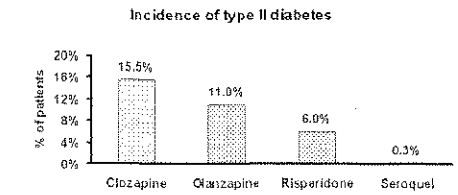
On this page

- A dosing study shows sedation incidence hardly increases, even at higher doses, and is comparable to haloperidol

About the studies

- Data on File S19 is from uncontrolled, placebo-controlled, and haloperidol-controlled studies of almost 3,000 patients taking Seroquel

Type II diabetes associated with atypical antipsychotic use



Cross-sectional study of 398 patients

Data on file AstraZeneca Canadian Guidelines on the Treatment of Diabetes 1999

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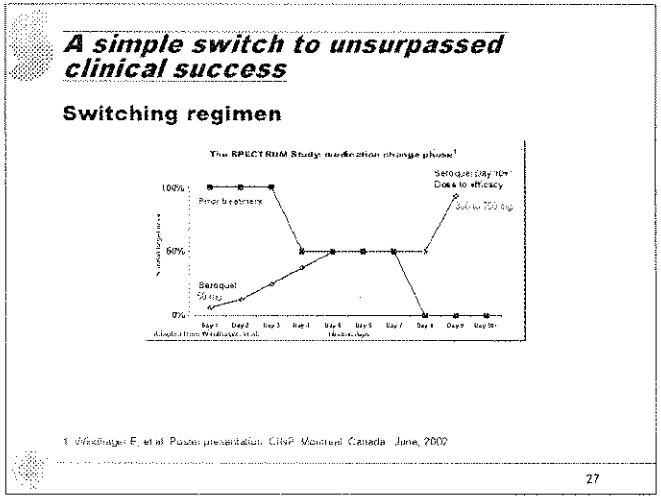


Starting patients who are taking another antipsychotic on Seroquel means simply cutting the current medication in half and increasing Seroquel in a few easy steps.

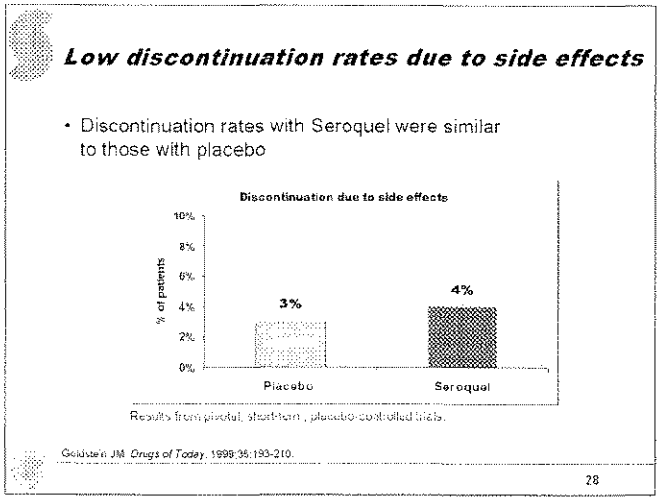
Key communication

Switching patients to Seroquel is simple.

On this page

- The schematic shows the switch protocol from the SPECTRUM study, in which patients were switched to Seroquel from a variety of other antipsychotics

SPECTRUM: Seroquel Patient Evaluation on Changing Treatment Relative to Usual Medication.



Seroquel tolerability is supported by its low discontinuation rates.

Key communication

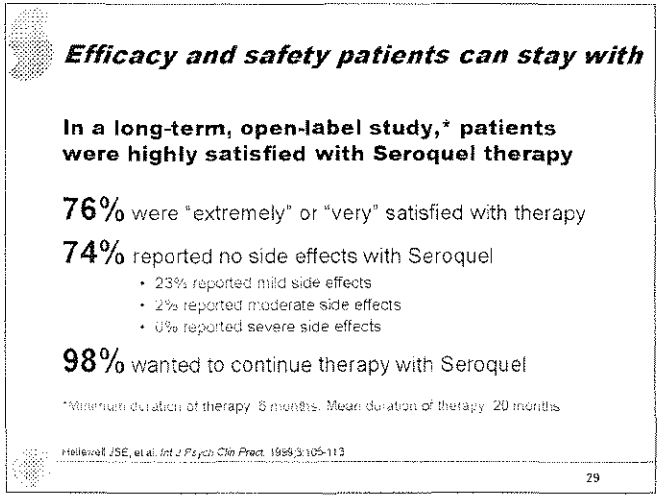
The percentage of patients stopping therapy with Seroquel due to side effects were essentially the same as with placebo.

On this page

- Simple and compelling evidence of Seroquel tolerability

About the study

- Pooled data from short-term trials



The efficacy and unique tolerability profile of Seroquel add up to patient satisfaction, providing therapy that patients can stay with long-term.

Key communication

The great majority of patients were highly satisfied with long-term Seroquel efficacy and tolerability. Almost all expressed interest in continuing therapy with Seroquel.

On this page

- The numbers link patient-reported satisfaction with efficacy and tolerability, with the conclusion that virtually all of them would continue therapy

About the study

- 129 patients from 12 countries who had been on Seroquel for at least 6 months and currently in open-label studies were asked to complete a questionnaire about satisfaction with therapy
- Mean treatment duration with Seroquel was 19.9 months, with 38% of patients on treatment for 31 to 42 months
- The most common characteristics patients reported that they liked about Seroquel were lack of side-effects or improvement in side effects caused by other medications
- 96% of patients who expressed a medication preference indicated a preference for Seroquel over previous antipsychotics for both efficacy and tolerability

EXHIBIT 8

ROUGH DRAFT{PRIVATE

}

QUETIAPINE

Joyce G. Small, M.D.[1]

Department of Psychiatry

Indiana University School of Medicine

Larue D. Carter Memorial Hospital

2601 Cold Spring Road

Indianapolis, IN 46222-2202

Telephone: 317/941-4000

FAX: 317/941-4014

1. Professor of Psychiatry

For publication in: Current Issues in the Psychopharmacology of Schizophrenia. Eds- Breir Alan, Bymaster Frank, Tollefson Gary, Tran Pierre, Herrera John Baltimore: Lippincott, Williams &

Wilkins.

QUETIAPINE

Introduction:

Seroquel (quetiapine fumarate, ICI 204,636), which was ~~developed~~ discovered in 1984 in the Zeneca (formerly ICI)Wilmington DE laboratories, is a dibenzothiazepine derivative with preclinical indications of antipsychotic activity without neurological side effects or elevations in prolactin. The structural formula is shown in Figure 1. Quetiapine exhibits binding properties similar to clozapine(1,2). Receptor data in animals showed quetiapine's greater affinity for 5-HT2 and 5-HT6 relative to D2 receptors. ~~although recent human evidence suggests that D2 binding may have been underestimated~~. Like clozapine, ~~Quetiapine, clozapine and other atypical neuroleptics occupy high levels of brain D2 receptors but are~~ quetiapine is loosely bound and readily displaced from the D2 receptor, particularly in the striatum(3), providing a mechanism for its low EPS liability~~.~~ It is selective for the A10 mesolimbic but not A9 nigrostriatal dopamine neurons. Unlike clozapine quetiapine has minimal affinity for M1 or D4 but binds strongly to the sigma receptor(4).

In this review clinical data from the pivotal placebo controlled

studies preceding the 1997 marketing of Seroquel and additional reports will be considered under headings of clinical efficacy, safety and tolerability, adverse events including movement disorders, laboratory abnormalities, pharmacokinetics and drug interactions, and therapeutic potential.

Clinical Efficacy:

Several thousand patients have been treated with quetiapine. Although all studies required DSM-III-R diagnoses of acute exacerbation of chronic or subchronic schizophrenia, all subjects typically had long histories of psychotic illness, multiple hospitalizations and previous treatment with standard and sometimes atypical antipsychotic drugs as well. Thus despite manifestations of acute psychosis, most patients could be regarded as chronically ill and relatively treatment resistant. Many of the trials were conducted in tertiary-care teaching centers. Moreover, women of child bearing potential were mostly excluded as were those unwilling to give consent. Hence they were a select group not truly representative of patients routinely encountered in clinical practice. Another consideration is that all conclusions available thus far are derived from industry supported studies without the benefit of confirmation by independent investigators(5).

There have been three placebo controlled pivotal Phase II and III

trials of quetiapine that utilized a substantial number of patients, randomized double-blind treatment assignment and trial durations of six weeks. The first was by Borison et al.(6) who studied 109 patients. Quetiapine was generally superior to placebo in an average dose of 307 mg. Small et al.(7) published results of a multicenter trial of 286 patients on low or high dose quetiapine OR placebo. The average low dose of 209 mg was no better than placebo but the mean high dose of 360 mg was superior to placebo. Arvanitis et al.(8) studied multiple doses of quetiapine compared with haloperidol and placebo. Dosages ranging from 150 to 750 mg were superior to placebo and equivalent to 12 mg of haloperidol. The lowest dose of 75 mg was ineffective. Another study by Peuskins and Link (9) compared quetiapine to chlorpromazine in 201 patients. The two drugs were therapeutically equivalent in mean doses of 407 mg of quetiapine and 384 mg of chlorpromazine. More details about each of these studies follow:

In the Borison et al., study overall therapeutic efficacy favored quetiapine. Although there were statistically significant differences between the treatment groups ($p \leq 0.05$) in favor of quetiapine at various times throughout the trial, differences at end point were not significant on the Brief Psychiatric Rating Scale (BPRS)(10) total score ($p=0.07$) or the anxiety/depression, anergia, thought disturbance, and hostile/suspiciousness factors. Differences in the BPRS positive

symptom cluster approached significance (p=0.06). The end of study Clinical Global Impression (CGI) rating (11) was likewise not significant (p=0.07). Statistical comparisons included all randomized patients who had efficacy data for at least one time interval after baseline with last observation carried forward (LOCF) for determinations at end point. More significant differences were observed earlier in the study in the quetiapine treated patients who improved steadily throughout the six week period whereas placebo subjects remained unchanged. BPRS total scores were significantly different on days 14, 28, and 35 as was the positive symptom cluster. Factor 3 - thought disturbance - was significantly better for quetiapine on days 28 and 35. CGI ratings showed significant differences between treatments on days 21, 28, and 35. The Scale for Assessment of Negative Symptoms (SANS) (12) showed significant group differences from day 21 onwards.

In the study by Small et al., comparing low and high dosage ranges of quetiapine with placebo, the low dose group and placebo were equivalent on global ratings and positive and negative symptoms. The high dose group at end point was significantly more improved on the CGI, the BPRS positive symptom cluster, and the SANS but not the Positive and Negative Syndrome Scale (PANSS)(13). These conclusions were also drawn from LOCF analyses.

Arvanitis et al., studied five fixed doses of quetiapine compared

with 12 mg of haloperidol and placebo. The lowest dose of 75 mg was not different than placebo whereas the quetiapine and haloperidol groups were equivalent at end point for the total BPRS scores and the positive symptom cluster and the CGI. Only the 300 mg dose of quetiapine and placebo scores were significantly better than haloperidol on the SANS. Based on this experience and the previous studies the optimal doses of quetiapine appear to range from 300 to 600 mg. However preferred amounts for management of primary negative symptoms and cognitive impairments to promote the best possible quality of life remain to be ascertained.

Additional randomized double blind trials without placebo conditions have been published. Peuskens and Link compared flexible doses of quetiapine with chlorpromazine showing that quetiapine was as effective as chlorpromazine on measures of both positive and negative symptoms. Sixty-five percent of quetiapine patients and 53% of chlorpromazine subjects achieved at least a 50 percent improvement in total BPRS total score at some point during the study, a statistically significant difference ($p = 0.04$) favoring quetiapine. In other trials dosing frequency was examined comparing two or three times daily schedules. Outcomes with bid and tid dosing were equivalent, corresponding with time courses of PET studies of decline in D2 and $5HT_2$ receptor occupancy but not plasma half-life(14).

Other evidence of therapeutic efficacy of quetiapine can be inferred from uncontrolled studies and case reports. Favorable results in two patients with psychosis and Parkinson's Disease were reported in which mental symptoms improved and Parkinsonism was not adversely affected(15). Another study examined the effectiveness of quetiapine in psychotic geriatric patients(16). An interim analysis was done in 150 patients after twelve weeks of treatment with average dosages of 75 to 100 mg. BPRS total scores and CGI global ratings improved progressively during the course of the trial with significant decreases from baseline. Results were comparable in patients with idiopathic or organic psychoses.

Cognitive impairment is another core feature of schizophrenia which may be benefited more by atypical than standard neuroleptics(17). Performance by schizophrenics and normal controls on a continuous performance test was studied before and after quetiapine therapy in the patients(18). They were significantly worse than normals at baseline but by the end of two months of treatment did not differ significantly from controls. The trial involved 10 patients who received quetiapine as part of other multicenter trials and a comparison group of twelve matched normal volunteers. More comprehensive trials with full neuropsychological test batteries have yet to be reported with quetiapine.

Since marketing of quetiapine abstracts, letters and case reports

about individual experiences have appeared at scientific meetings, in journals and on the Internet. Favorable results were reported in an adolescent with childhood onset schizophrenia who had not responded satisfactorily to other atypical neuroleptics i.e., risperidone and olanzapine(19). Cognitive improvement accompanying treatment with Seroquel was described in a man with chronic schizophrenia(20). Positive comments have appeared on the Internet, mentioning advantages with quetiapine mostly due to fewer side effects(21). Recent presentations have included therapeutic benefits in Alzheimer's disease associated with psychosis,(22) in adolescent patients,(23) and in schizophrenic patients displaying hostility, aggressive behavior and affective symptoms(24). Surveys of caretaker and patient satisfaction indicated a high rate of acceptability of atypical neuroleptics in general and quetiapine in particular with improved quality of life(25,26). Another study was presented indicating beneficial results with quetiapine in Parkinsonian patients on both psychotic and motor abnormalities(27). Comparative studies of quetiapine with other atypical antipsychotic drugs are beginning to appear. An open-label four month trial comparing quetiapine and risperidone in 751 outpatients (28) showed improvement on both drugs with advantages for quetiapine on depression ratings and the CGI. There were no statistically significant differences on ratings of positive or negative schizophrenic symptomatology.

To summarize the data on therapeutic efficacy: relief of positive symptoms appears comparable to standard neuroleptics, primarily haloperidol. Effects on negative symptoms are less robust but they appear to resolve to a greater extent than with placebo or standard neuroleptics. Data on cognitive dysfunctions and quality of life issues are sparse. It must be kept in mind that the bulk of the information about efficacy is limited to six weeks of treatment with few controlled observations for longer time periods. Moreover information in schizoaffective and bipolar disorders, the elderly and pediatric populations and medically compromised patients is minimal and no data are published to date on first episode or refractory schizophrenia.

Safety and Tolerability:

Quetiapine has a good overall safety and tolerability profile with few patients discontinuing from studies due to adverse effects. It has an especially low incidence of extrapyramidal side effects (EPS) with values comparable to placebo and no evidence of a dose response curve. This was also reflected in the minimal use of concomitant anticholinergic medications. The primary reason for early dropouts from pivotal studies was treatment failure as would be expected in chronically ill, hospitalized schizophrenic patients. Correspondingly, the most frequently reported adverse events were common accompaniments of schizophrenic exacerbations

such as agitation and sleep disturbances.

The controlled trials yielded similar adverse event profiles with quetiapine with most complaints rated as mild or moderate. Agitation, somnolence, and headache were the most commonly reported side effects. Somnolence was more common with quetiapine than placebo but similar for quetiapine and low to moderate doses of chlorpromazine. Postural hypotension was encountered infrequently with quetiapine in the placebo controlled trials, occurring three times more often with the chlorpromazine comparator. Other less frequently encountered events included constipation, dry mouth, and tachycardia. Case reports of quetiapine overdoses also attest to its safety(29,30). Sinus tachycardia and sedation were the major effects of acute overdosages from 4700 to over 10,000 mg which resolved uneventfully with supportive care.

Adverse Events:

There is a wide spectrum of potential adverse events with antipsychotic drug therapy. Neurological side effects are the major category which includes Parkinsonism, dystonia, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, seizures and epileptiform EEG features. Impaired cognition, psychotic, decompensation, abnormalities in mood, behavioral worsening and obsessive compulsive manifestations are other CNS effects. Further

all antipsychotics can produce adverse withdrawal symptoms if suddenly or rapidly discontinued with psychotic decompensation, cholinergic rebound, emergent dyskinesias, and general malaise. Early relapse may be more problematic with atypical than standard neuroleptics because of loose binding and rapid release from D2 receptor occupancy in the former(31).

Significant endocrinological abnormalities may develop due to hypogonadism produced by hyperprolactinemia with galactorrhea, menstrual irregularities, sexual dysfunctions and long term risks of osteoporosis, breast cancer and heart disease. Disturbances in glucose regulation may accompany atypical neuroleptic therapy. Asymptomatic deviations in thyroid function tests have also been reported. Weight gain is a common problem. Other side effects involve cardiovascular events such as prolonged QTc interval, postural hypotension, tachycardia and other arrhythmias. Decreased bowel motility, cholestatic jaundice and other gastrointestinal problems can occur. Transient elevations in hepatic transaminase activity have been observed, generally without clinical manifestations.

Unlike the case with clozapine, agranulocytosis and other hematologic abnormalities are not frequently associated with standard or other atypical antipsychotic agents. Nonetheless all of these drugs can impact adversely on multiple organ systems

giving rise to ophthalmologic, dermatologic, allergic and other complications.

Neurological Effects:

Extrapyramidal side effects (EPS) did not distinguish between quetiapine and placebo in the three placebo controlled trials cited previously as measured by Simpson-Angus Scale (SAS) (32) scores at endpoint. This was also reflected in the minimal use of anticholinergic agents for treatment emergent EPS. In the Arvanitis et al. study twelve percent of patients on quetiapine were given anticholinergic drugs for control of EPS compared to 14% on placebo and 48% on haloperidol. The incidence of akathisia measured by the Barnes Scale (33) was the same for quetiapine as with placebo. In the quetiapine - chlorpromazine comparison there were low levels of EPS in both treatment groups. Among the chlorpromazine subjects one patient was withdrawn because of an acute dystonic reaction and more anticholinergic medications were prescribed. Quetiapine and placebo Barnes scores tended to improve from baseline, more with higher quetiapine doses, whereas the haloperidol group worsened. It can be concluded that quetiapine rarely produces EPS. However two cases who experienced EPS with relatively low doses of quetiapine were reported on the Internet(21). One was an Asian woman and the other a man diagnosed as bipolar.

Seroquel has not been available long enough to ascertain its liability for producing tardive dyskinesia (TD). Judging from data on other atypical neuroleptics, the risk can be predicted to be substantially less than with standard neuroleptics. It is also not yet clear whether quetiapine will suppress abnormal involuntary movements. Likewise the risks of neuroleptic malignant syndrome are unknown although cases with several other atypical antipsychotic agents have been reported.

Seizures are another complication of neuroleptic therapy, particularly with clozapine(34). With some exceptions the incidence of seizures is directly proportional to the degree of sedation associated with the drug as well as other factors such as dosage and speed of titration, seizure threshold, concomitant medications, etc.(35). The incidence of seizures with clozapine has been reported as 1.1% whereas clinical trial data for olanzapine yielded 0.9%, risperidone 0.3% and quetiapine 0.8% (36). Epileptiform EEG features in association with clozapine treatment may warn of impending seizures if the dosage continues to increase. However they may also be a favorable prognostic sign(37).

Other research has involved quantitative EEG (QEEG). Studies examining waking EEG and sensory evoked potentials before and after single doses and chronic intake of standard neuroleptics have been

accomplished in schizophrenic patients. QEEG changes have been reported in specific EEG frequency bands with significant associations with plasma neuroleptic levels and indications of therapeutic response.(38,39) QEEG investigations with atypical agents are in progress. Small et al.(40) reported significant negative rank order correlations between D2 receptor affinities and spectral energy in the theta band (4 to 8 Hertz (Hz)) with lowest amplitudes after 4-6 weeks of optimal therapeutic doses for haloperidol followed by risperidone, olanzapine, quetiapine, and clozapine. However these determinations were based upon animal data which are not directly applicable to humans. There were positive associations between the purported degree of histamine receptor binding of the four atypical neuroleptics with highest amplitudes in the fast beta-2 band (18-30 Hz) with quetiapine followed by olanzapine, clozapine, and risperidone.

Other CNS adverse effects include a range of impairments that can be encompassed under the rubric "behavioral toxicity". These reactions may be idiosyncratic or related to dose and timing. Atypical neuroleptics are particularly prone to induce or expose obsessive-compulsive features(41,42). This has not yet been reported with quetiapine but has been observed by the author. Receptor data suggest that withdrawal symptoms would be likely to occur with quetiapine. However abrupt withdrawal of quetiapine

with switchover to standard neuroleptics was associated with psychotic relapse in only 2 of 50 patients studied by Goldstein without associated physical problems(43). Higher than optimal dosages can be associated with increased agitation and other indications of psychotic worsening as well as other side effects. Sleep disturbances with either sedation or insomnia may accompany drug therapy but may also be features of underlying psychosis.

Endocrinological effects:

There were no significant elevations in serum prolactin in the pivotal trials described previously and in some instances quetiapine was associated with reduced levels from baseline. Prolactin levels were significantly higher with both chlorpromazine and haloperidol. There were no significant differences between quetiapine and placebo in either men or women. In the absence of hyperprolactinemia problems such as gynecomastia, menstrual irregularities, impotence, etc. would not be expected although most trial durations were not long enough to evaluate these issues. Likewise reproductive and neonatal difficulties have not been reported to date.

However weight gain was an adverse event experienced by two percent of quetiapine patients in the placebo controlled studies. Clinically significant weight gain, that is more than 7 percent

increase in body weight, was seen more with quetiapine than placebo - 24 percent compared with four percent in the Borison et al. study. Weight gain appeared to be dose related in the Small et al. and Arvanitis et al., trials ranging from five percent for placebo, fifteen percent for low dose and twenty-four percent with high dose quetiapine in the former. Likewise weight gain in the Arvanitis et al. study was proportional to dosage and exceeded amounts with haloperidol and placebo. Twenty-seven percent of quetiapine treated patients had significant weight gain compared with eighteen percent with chlorpromazine reported by Peuskens and Link.

Adverse effects of atypical antipsychotics upon glucose regulation have been recognized recently mostly with clozapine. Hägg et al.(44) compared clozapine patients with those on depot standard neuroleptics and found hyperglycemia in thirty-three percent with clozapine and nineteen percent with traditional antipsychotics ($p=.07$). Non-insulin-dependent diabetes mellitus or impaired glucose tolerance occurred in twenty-one percent of the clozapine patients versus 9.5 percent of those taking standard neuroleptics ($p=.06$). Likewise the incidence for clozapine was over three times the expected number of cases based on population surveys. New onset diabetes has also been reported with olanzapine(45). It appears that atypical neuroleptics may promote weight gain, insulin insensitivity and glucose intolerance by virtue of their antagonism of histamine and serotonin receptors. African-Americans are

particularly vulnerable to these effects and individuals with personal or family histories of diabetes mellitus or obesity. As clozapine, olanzapine and quetiapine cause the most weight gain, these drugs may be most likely to induce diabetes. Case reports with quetiapine have not appeared so far.

Quetiapine was associated with small reductions in mean total T4 and occasionally T3 but these were not associated with concomitant elevations of TSH or any indications of clinical hypothyroidism. Maximal reductions occurred in the first two to four weeks of treatment with no further decline with continued intake. In nearly all instances discontinuation of quetiapine was followed with prompt reversal of effects on both total and free thyroxine.

Cardiovascular, gastrointestinal, and hematologic abnormalities:

Quetiapine exerts some cardiovascular effects such as orthostatic hypotension and dizziness. These usually occur during the initial period of dosage titration and seldom require discontinuation. EKG recordings showed little change in QTc intervals and there was no relationship between plasma levels of quetiapine and the QTc changes. Quetiapine appears to have minimal proarrhythmic activity. However in both reported cases of overdosage there was sustained sinus tachycardia persisting up to 48 hours. A further disclaimer should be added that experience has yet to be obtained

in patients with preexisting heart disease and EKG abnormalities. The major gastrointestinal effects of quetiapine are mild transient, reversible and asymptomatic elevations in serum transaminase (ALT, AST) or gamma-glutamyl/transferase levels. These abnormalities did not exceed five times the upper limits of the normal range for the laboratory assay and were generally reversible despite continued treatment. Constipation was endorsed as a problem in fewer than ten percent of patients, similar to the incidence with placebo. However weight gain was a significant issue as discussed previously.

Hematologic abnormalities are of particular concern in the light of the experience with clozapine. No cases of granulocytopenia have been noted to date nor any deaths that could have been the result of undetected agranulocytosis. Although there appear to be no hematologic problems with quetiapine it should be recognized that patients with preexisting abnormalities or individuals predisposed to these complications were excluded from the systematic trials. Moreover combinations of quetiapine with other agents have yet to be studied.

Ophthalmologic effects:

Quetiapine was associated with the development of cataracts in dogs that received quetiapine at four times the maximum recommended

human dose for six to twelve months. No evidence of cataracts appeared in a comparable study of monkeys at even higher doses and none have been observed in humans. Nevertheless labeling for now recommends that periodic slit-lamp examinations be done before quetiapine treatment and at six month intervals thereafter. Complicating this situation is the high incidence of cataracts in patients with schizophrenia as well as longitudinal changes that occur with advancing chronological age(46).

Pharmacokinetics and Drug Interactions:

The plasma half-life of quetiapine is 6 to 8 hours but the half-life of receptor occupancy may be longer as mentioned earlier. Gefvert et al.(47) compared plasma half-life and D2 and 5-HT2 receptor occupancies finding that the latter declined more slowly than plasma levels, particularly 5-HT2. Fleischhacker et al. (48) compared twice and three times daily dosage regimens of quetiapine and observed a few advantages for twice daily dosing, results supported by PET studies of receptor occupancy.

Quetiapine is rapidly absorbed after oral administration with peak blood levels in 1 to 1-1/2 hours. It appears to be widely distributed in tissues and extensively metabolized in the liver with only a small amount of the parent compound excreted in the urine. The major metabolic pathway involves sulphoxidation by

cytochrome P450 3A4 although CYP 2D6 may also play a role(49). Consequently elevated plasma levels of quetiapine can be anticipated with co-administration of enzyme inhibiting drugs such as ketoconazole, erythromycin, nefazodone, fluvoxamine, and some other antidepressants. 3A4 enzyme inducers such as phenytoin and to a lesser extent thioridazine can increase both clearance and dosage requirements but quetiapine levels will likely rise when the inducer is stopped.

Therapeutic Potential:

Results from randomized, double-blind clinical trials conducted thus far indicate that a wide dosage range of quetiapine is well tolerated and effective in the treatment of positive and negative symptoms of schizophrenic exacerbations. Preclinical and clinical data support its status as an atypical antipsychotic drug with few Parkinsonian, extrapyramidal or other neurological side effects. Although comparative data are not yet available quetiapine may offer the widest dosage range with fewest neurological side effects of all the marketed atypicals. Lack of effects on prolactin predicts few if any sexual dysfunctions and other endocrinological side effects that impinge upon patient compliance. The absence of cardiovascular effects is another desirable feature that may reduce or eliminate the need for dosage titration, although this must be

investigated further. Likewise its weak anticholinergic activity offers potential advantages for patients with cognitive impairments. However weight gain is a significant adverse effect that may limit acceptance as will the required twice daily oral dosing schedule and the ophthalmologic examinations.

Quetiapine's eventual place relative to the other atypical neuroleptics remains to be established. Studies of these applications are appearing rapidly at national and international scientific meetings. Clinical trials in progress include studies of nursing home residents with Alzheimer's dementia and psychosis, studies of psychotic adolescent patients, further investigators of Parkinsonism and combinations of quetiapine and carbamazepine(50).

Data have been already collected from industry supported multicenter trials of treatment refractory schizophrenic patients which should be analyzed and reported in the near future. In this regard an abstract from Japan on refractory patients appeared in a recent program(51). Numerous other investigations are in progress which should soon establish the place of quetiapine in the therapeutic armamentarium.

Figure 1. Structural formula.

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EXHIBIT 9

Expert Report of Donna K. Arnett, Ph.D.

A. Brief Report of Professional Qualifications

I am an epidemiologist with more than 20 years of experience in the design and conduct of experimental and observational epidemiological studies, including clinical trials, family studies, cross-sectional surveys, cohort, and case-control studies. I am Professor and Chair of Epidemiology at the University of Alabama at Birmingham, Department of Epidemiology. I am a Fellow of the American Heart Association and the American College of Epidemiology, and an Elected Member of the American Epidemiology Society. I have served as an Associate Editor for the *American Journal of Epidemiology* since 1996 and as an Editor since 2004. I currently serve as a Guest Editor and as relief Guest Editor-in-Chief for *Circulation*. I am routinely asked to evaluate epidemiological research studies for publication in peer-reviewed journals, including the *New England Journal of Medicine* and the *Journal of the American Medical Association*. I have served on numerous National Institutes of Health (NIH) review panels for epidemiological research. For the past two years, I have served as Chair for the Cardiovascular and Sleep Epidemiology Study Section (CASE) for the National Institutes of Health.

My principle professional interests include cardiovascular and metabolic disease epidemiology, genetic epidemiology, and pharmacogenetics. I have published more than 225 peer-reviewed articles and more than 12 book chapters or invited review papers.

Since 1994, I have designed and taught graduate level courses in fundamental and advanced concepts of epidemiology, methodological and theoretical aspects of epidemiology, and grant writing. From 1998-2001, I served as Chair of the Epidemiology Master's Degree Program at the University of Minnesota and as Director for the National Heart, Lung, and Blood Institute funded Training Program in Cardiovascular Genetic Epidemiology. For the past 10 years, I have taught a two-week summer course in Epidemiology and Prevention to physicians and other health care professionals for the American Heart Association and Centers for Disease Control.

A copy of my curriculum vitae is attached for additional detail.

B. Brief Overview of Principles of Epidemiology

Randomized, double-masked, placebo-controlled clinical trials are the optimal design for testing a hypothesized association between an exposure (or treatment) and disease because such studies offer the best control for confounding (i.e., variables that are associated with the disease and associated with the exposure) and provide for the optimal test for temporality (i.e., exposure precedes disease). Placebo controlled studies are the gold standard for evaluating the risks and benefits of a new treatment. During a clinical trial, four general reasons could explain clinical improvement in a

participant's condition: (1) natural history of the disease; (2) specific effects of the treatment under investigation; (3) regression to the mean; and (4) placebo effect. A study without a placebo control cannot differentiate amongst the prior 3 conditions. Active comparator randomized clinical trials are frequently used once a known treatment is available since withholding treatment from a diseased group could be unethical; however, there are methodological limitations of trials that use an active control. For example, there can be variable responses to drugs in some populations, unpredictable and small effects, and spontaneous improvements which with an active (rather than a placebo) control may mask the full effect of the drug under investigation.

Many epidemiological studies are observational and provide an assessment of a relation between an exposure and disease. Because of the observational nature of these studies, exposures are not "randomly-assigned" to study volunteers, and hence, factors that may be associated with the exposure of interest, and also independent predictors of the disease, may confound the observed relation between the exposure and disease. The best observational design to test a hypothesized association between exposure and disease is a cohort study. Cohort studies can be conducted either prospectively or retrospectively. Cohort studies are similar conceptually to clinical trials in that subjects are followed for the occurrence of endpoints. Therefore, temporality between the exposure and the endpoint can be conclusively evaluated. The availability of large administrative databases has prompted a number of cohort studies to evaluate adverse exposures, including pharmacological exposures, in relation to disease. The benefits of these types of cohort studies include their cost efficiency and ease of implementation. For example, pharmacy records can be linked to clinical records to assess a hypothesized association between a particular drug exposure and disease.

Case-control studies are also hypothesis-testing studies, and they rely on design qualities that, if done correctly, provide for an estimation of the exposure-disease relationship in a cost-efficient way. In a case-control study, diseased individuals are sampled (i.e., cases) as are non-diseased individuals (i.e., controls), and subjects are classified with respect to exposure. The effect measure used is the ratio of the exposure odds in cases compared to the exposure odds in controls. Conceptually, the case-control study can be thought of as nested within a population cohort, and if two important criteria are met, provide a valid estimate of the disease odds ratio. For excellent internal validity, a case-control study requires that exposure must measured in all cases (or a representative sample of cases that reflects the true exposure odds of all cases), and that the sample of the non-diseased members of the source population that generated the cases reflect the exposure odds of the population. If these conditions are met, then the exposure odds ratio will be equal to the disease odds ratio that can be calculated from a cohort study. In practice, these conditions are challenging to meet except in the case of the nested case-control studies, where the exposure odds can be accurately measured using previously collected data and/or specimens. Nested case-control studies overcome two other potential biases common to the case-control studies, namely, temporality and recall bias. Temporality is a concern in non-nested case-control studies because exposure ascertainment is

determined after disease onset. Another potential bias unique to non-nested case-control studies is recall bias, where cases are more likely than controls to recall prior exposures because of their disease.

C. Review of the Evidence for Effects of Seroquel on Metabolic Risk, including Weight Gain, Hypertriglyceridemia, Insulin Resistance, and Diabetes

The basis for my opinions expressed herein is derived from my education, training, research, experience, and review of the Seroquel New Drug Application (NDA) to the Food and Drug Administration, internal Astra Zeneca documents, the peer-reviewed medical literature, and other publicly available documents concerning Seroquel and its relationship to weight gain and other metabolic risks. In developing my opinions in this case, I am relying primarily upon the Astra Zeneca NDA application and the related published literature, published cohort and nested case-control studies, and meta-analyses of published studies. I have spent over 80 hours reviewing literature and documents related to Seroquel.

Based upon my review of the above specified documents, I have developed the following opinions in this case: (1) Seroquel leads to clinically significant and relevant metabolic risk, including weight gain and other metabolic complications, including but not limited to hypertriglyceridemia, insulin resistance, and diabetes; (2) the metabolic risks from Seroquel appear shortly after treatment and throughout treatment; (3) Astra Zeneca should have made the data presentation clearer within the New Drug Approval application and included the data regarding metabolic risk within scientific publications of the Phase II and Phase III randomized clinical trials in order to warn the FDA, future patients and physicians about metabolic risks associated with Seroquel; (4) the metabolic risks associated with Seroquel outweigh the benefits of treatment; and (5) Astra Zeneca promoted Seroquel as metabolically neutral when there was insufficient evidence to support this claim but substantial evidence that the drug in fact caused weight gain and other metabolic derangements (6) Astra Zeneca withheld support for studies that could have demonstrated Seroquel's metabolic risk relative to other atypical antipsychotics. I have developed these opinions utilizing the normal methodology that I exercise as an epidemiologist in the ordinary scope of my practice. Further, I state these opinions to a reasonable degree of scientific certainty.

C.1. Overview: The Effect of Seroquel on Weight Gain and Other Metabolic Derangements

Seroquel causes weight gain and other metabolic toxicities through stimulation of the hypothalamic AMP activated protein kinase (AMPK). AMPK is responsible for maintaining energy balance and the regulation of food intake. Seroquel blocks histamine H1 receptors, the receptors responsible for the inflammatory response which then stimulates AMPK. In addition to the effects on H1 receptors, Seroquel affects insulin action and metabolism directly in the cell, leading to insulin resistance

and alterations in lipogenesis and lipolysis, which ultimately cause progressive lipid accumulation.

Weight gain can lead to reductions in patient compliance with the medication which could lead to poor clinical outcomes. Weight gain is an important concern of Seroquel treatment, and in particular among schizophrenic individuals since there is an association between schizophrenia and Type II diabetes mellitus, and weight gain is an important risk factor for diabetes development. Weight gain is also an important determinant of other metabolic toxicities, such as hypertriglyceridemia, hypertension, and insulin resistance, all part of the metabolic syndrome. Moreover, once weight has been gained, it is challenging to lose, and this is a large concern for schizophrenic patients who are not typically capable of undertaking lifestyle management to maintain or to lose weight.

There is unequivocal and consistent evidence that Seroquel treatment leads to clinically and statistically significant increases in weight, that the onset of the weight gain occurs shortly after the beginning of treatment and progresses with increased duration of treatment, and that the weight gain is proportionate to the dose ingested. Significant weight gain was observed during the Phase II and III trials and subsequently demonstrated throughout the developmental program of Seroquel for other treatment indications. In addition, other components of the metabolic syndrome (i.e., hyperinsulinemia, hypertriglyceridemia) were similarly observed during the development of Seroquel, and increased incidence of diabetes has been observed with Seroquel treatment. The justification for this opinion follows.

C.1.1. Weight Gain in Response to Seroquel Treatment

The New Drug Application for Seroquel was submitted to the FDA in July, 1996. According to the Integrated Safety Report filed as a part of the NDA, weight and vital signs were collected on the same case report form and were summarized together in the safety report to the FDA. In fact, according to the majority of protocols reviewed, weight for the Phase II and III trials was collected at each visit. Results presented in the Integrated Safety Report are restricted to the analysis which required that subjects who were included in the tabulations had both baseline and post-baseline observations available. Clinically significant weight gain was defined by a gain of 7% of the baseline body weight (approximately 10 pounds for a 150 pound individual).

In the Phase II and III trials, the mean age of the trial participants was 38 years, and the mean body weight was normal (76 kg or 168 lbs). A total of 2162 schizophrenic patients were exposed to Seroquel with doses ranging from 50 to 800 mg/day administered between two and four times daily. Of the 2162 subjects, 1710 were from Phase II and III controlled trials and 454 were from new Seroquel exposures from the uncontrolled trials and were available for analysis. As of June 1, 1995, 407 subjects had been exposed to Seroquel for 6 months or longer and only 1 subject for 2 years or longer; 110 subjects were treated for one year or longer. As stated on page

119 of the report, "In the Phase II and III placebo-controlled trials, Seroquel was associated with a statistically significant weight gain (p=0.0471)." Additionally, from the short term placebo-controlled trials, Astra Zeneca stated that the mean weight gain for Seroquel-treated patients was 2.2 kg (4.85 pounds) greater than the mean weight increase for placebo-treated patients. The range of weight gain was markedly higher for the Seroquel treated than the placebo treated patients, indicating that the distribution of weight gain was non-normal. Therefore, median weight change would have been the optimal measure of central tendency, but median weight change was not provided (in contrast to other vital sign measures that were provided as medians). Had the median, rather than the mean, been reported, the findings regarding the differences between Seroquel and placebo would have been even more dramatic. More detail regarding individual studies is provided below.

The following table describes the studies included in the NDA, and the status of vital signs collected in each. Placebo controlled trials are indicated by **bold** type. Uncontrolled trials are indicated by *italics*. Active comparator trials are indicated by underlined text. Trial 0012 was a low dose Seroquel study and limited data were provided in the Integrated Safety report for this study, although the data provided were indicative of weight increases with treatment.

Vital signs and weight assessments by trial (integrated Phase II-III trials)

	0004	*0005*	**0006**	0007	**0008**	0012	**0013**	0014	0015	*0048*	*LTE*
Pulse	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*		X	X	X	X	X	X	X	X	X	X
Respiratory	X	X	X		X						
Temperature		X	X	X	X	X		X		X	US
Weight	X	X	X	X	X	X	X	X	X	X	X

* All measures were taken while subjects were seated.
* Unless otherwise noted, readings were taken for both supine and standing systolic and diastolic blood pressures.
+ Only supine readings were taken for Trial 0007.
** Respiration readings were taken while subjects were in the supine position unless otherwise noted.

Data for studies 0004, 0006, 0008, and 0013 were only provided in summary form. In these trials combined, 89/391 (23%) of Seroquel treated subjects had clinically significant weight gain compared to 11/178 (6%) of placebo-treated subjects. This resulted in a relative risk for clinically significant weight gain with treatment of **3.68** (p<.0001, 95% CI 2.1-6.7).

For Study 13 alone, clinically significant weight gain was observed in 2/51 (6%) for placebo, 2/52 (4%) for haldoperidol, 6/53 (11%), 8/48 (17%), 5/52 (10%), 8/51 (16%), 7/54 (13%) for Seroquel 75 mg, 150 mg, 300 mg, 600 mg, and 750 mg, respectively. In comparing low dose Seroquel (75 or 150 mg) versus placebo, the relative risk of weight gain was **3.54** (p=.06, 95% CI .95-16.1), and contrasting high dose (the dose recommended for schizophrenia), the relative risk of weight gain versus placebo was **4.77** (p=.012, 95% CI 1.34-18.2). This provides strong evidence

for dose response, a criterion frequently invoked to determine causation, and also indicates that Seroquel results in increased risk of clinically significant weight gain.

For Study 0013 and 0014 combined, clinically significant weight gain occurred in 70/354 (19.8%) in the Seroquel treated subjects versus 18/236 (7.6%) in the hadoperidol treated subjects (relative risk **2.61**; 95% confidence interval 1.61 – 2.42, p<.0001).

For Study 0007, clinically significant weight gain occurred in 28/100 Seroquel treated subjects compared to 19/99 of the chlorpromazine treated subjects (**RR=1.47**, p=-0.14, 95% CI 0.88-2.44). This active comparator study indicated that Seroquel's weight gain was greater than that of another atypical antipsychotic. This active comparator was not used again in subsequent trials presented in the NDA.

In summary, for these short-term placebo trials, the relative risk for a clinically significant increase in weight ranged from 2.61 to 4.77, indicating a strong and consistent increased risk, and for the active comparisons, a modest to strong increased risk for weight gain compared to chlorpromazine and haldoperidol.

Study 0015 was the long-term, 52-week study, implemented to evaluate the long-term efficacy and safety of Seroquel compared to haldoperidol for treatment of schizophrenia. In this study, Seroquel was associated with a statistically significant increase in weight gain that was dose-dependent and time-dependent (i.e., the longer the treatment, the greater the weight gain). The difference in the mean weight gain was 3.0 kg between treatment groups (+1.6 kg for Seroquel versus -1.4 kg for haldoperidol). Clinically significant weight gain occurred in 50/209 (23.9%) of the Seroquel participants compared to 4/38 (10.5%) of the haldoperidol-treated subjects (relative risk=2.27, p=0.066, 95% CI=0.94-7.55). As stated in the Integrated Safety Report "In general, mean weight increases from baseline for quetiapine-treated subjects were greater at Week 52 for subjects completing the trial (ranging from 2.05 to 8.52 kg) compared with the increases seen at final evaluation (Week 52 or withdrawal), suggesting a trend for subjects to continue gaining weight over time." Also stated in the Integrated Safety Report "The percentage of subjects with clinically significant increases from baseline in weight increased as the dose level of quetiapine increased (for the 75-, 300-, and 600-mg dose groups, 15.2%, 22.9%, and 32.9% of subjects had significantly high changes)." This dose-response was statistically significant. The findings from this long-term study confirm findings of the short-term studies and also suggest that weight gain continues with treatment duration.

In the uncontrolled trials (0005, 0048, and OLE), 27.5% of Seroquel-treated subjects had a clinically significant high weight gain, comparable to the findings in the controlled trials and the long-term controlled trial for Seroquel-exposed participants (Study 0015 cited previously, i.e., 23.9%).

In addition to these controlled and uncontrolled trials included in the NDA application, there were indications from the long-term extensions of the trials that weight gain was persistent throughout follow-up and increased with time, indicating

that prolonged treatment with Seroquel could lead to substantially increased risk of metabolic toxicity. With increased follow up, data later presented during the observed long-term extensions showed that 37.2% of Seroquel-exposed patients had clinically significant weight gain at some point during follow up. Weight gain increased with increased exposure duration: mean weight change compared to baseline weight increased by 3.8 (± 9.0) kg at week 65, 4.4 (± 9.6) kg at week 104, 5.7 (± 10.9) kg at week 156, and 6.7 to 7.3 (± 9.9-13.1) kg at weeks 208 - 260. If presented as median weight gain, this substantial weight gain would have undoubtedly been much larger.

There are two methodological concerns that, with a degree of scientific certainty, resulted in underestimates of the true effect of Seroquel on weight gain in these studies. First, the studies provided in the NDA had consistently high drop-out rates for Seroquel. This is an important characteristic to define the internal validity of a study. Among the 2162 subjects randomized to (n=1710) or treated in uncontrolled trials (n=454), 80.1% withdrew, and the rate was much higher than the 42% for the active comparators or 61.2% for placebo. This has important implications for the interpretation of results related to weight gain or other metabolic abnormalities. Weight gain is a major contributor to non-compliance, and in aggregate in the Phase II and III program, weight gain was associated with greater drop-outs. Therefore, the result reported from these studies almost surely underestimates the true impact of Seroquel on weight gain. Second, many of the studies conducted restricted weight as an inclusion criterion, generally between 100 and 230 pounds. Had heavier subjects been included, it is likely that the weight gain would have been even greater. Since these subjects were excluded, it is unclear whether Seroquel would have been safe in overweight and obese subjects (i.e., the studies are not generalizeable to these subjects).

A metabolic cause for concern regarding the weight data presented in the NDA is the consistent pattern for reductions in thyroid hormone levels that occurred with Seroquel treatment. Low levels of thyroid hormone are associated with greater body weight. Each trial presented in the Table above collected at least one measure of thyroid function. As stated in the Integrated Safety Report, "Consistent laboratory data suggest that quetiapine treatment tends to reduce thyroid hormone plasma levels, primarily total T4 and free T4 with smaller decreases seen in total T3 and reverse T3... Both total T4 and free T4 mean values are reduced and the incidence of significantly low values is increased in quetiapine-treated subjects compared both to placebo- and haloperidol-treated subjects. Results from Trials 0013 and 0015 indicate that the reductions in thyroid hormone levels are dose-related, that the onset of the reductions may occur within the first few days of treatment." Note that the definition of abnormalities for any of the thyroid hormone levels was less than 0.8 times the lower limits of normal or greater than 1.2 times the upper limit of normal. The Integrated Safety Report dismisses these thyroid changes as clinically irrelevant since the thyroid stimulating hormone did not significantly increase. However, because most of the studies were short term, the design may have precluded the development of an increased TSH.

Finally, weight was measured at almost every visit along with the vital signs. Yet detailed week-by-week data could not be found in the Integrated Safety Results. No data were provided in the published literature across the time course of the studies. This is particularly important given the very large drop-out rates that occurred consistently throughout the studies provided in the NDA. It is likely, given the consistent weight increases seen in every Phase II and III study conducted and summarized in the NDA that weight increased among those that subsequently dropped out, and therefore, findings that included subjects who dropped out could have made the findings even less favorable for Seroquel.

Additional studies from the AZ website conducted after the NDA was submitted were evaluated for weight change (based on data provided only on the AstraZeneca website) and showed the consistent pattern of weight increase seen with studies included in the NDA. Data are only tabulated for the first 11 studies listed on the website since the results were consistent with those observed as part of the NDA.

Table 1. Weight Change in AstraZeneca Studies

Study Number	Start – End Date	Results for Metabolic Risk Factors
0039	03/16/98 – 02/03/00	Clinically significant weight gain in 6% of Seroquel, 5% of haldoperidol, and 2% of placebo treated subjects.
0050	05/02/96 - 05/21/99	6 subjects with hypothyroidism on Seroquel; none on haldoperidol
0099	08/09/00 - 11/26/01	Seroquel-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group.
0100	11/08/00 – 01/25/02	Clinically significant weight gain in 10.4% of Seroquel subjects versus 3.9% of placebo subjects (relative risk=2.67)
0104	01/07/01 – 04/25/02	Seroquel subjects gained 2.1 kg versus a loss of 0.1 kg in placebo subjects and a gain of 0.2 kg in haldoperidol subjects
0105	04/03/01 – 05/27/02	Weight gain 3.3 kg in Seroquel vs. 0.3 kg in placebo; clinically significant weight gain in 15% versus 1%, respectively (relative risk=15)
0043	06/28/01 – 09/04/02	Both weight gain and glucose significantly increased (no data provided)
0046	No dates provided	Clinically significant weight gain occurred in 12-15% of Seroquel treated subjects (100-200 mg) versus 15% of placebo treated subjects (relative risk = 0.8 to 1.0)
0049	09/30/02 – 09/17/03	Weight increased 1.7% and 6.1% in 300 and 600 mg Seroquel, respectively, vs. 0.6% in placebo (relative risk 2.8 and 10.2, respectively)
D1447C-0001	08/31/05 - 05/24/07	Seroquel mean weight gain ranged from 0.4 to

		1.3 kg across the doses used compared to placebo (-0.4 kg). Clinically significant weight gain occurred in 12.0 to 15.4% of Seroquel groups compared to 2.9% in the placebo group (relative risk 4.2 – 5.3).
D1447C-0135	06/30/04 – 08/26/05	Weight increased 4.1 kg and 5.4 kg in Seroquel 300 mg and 600 mg treated subjects vs. 1.8 kg in placebo subjects

In aggregate, the evidence from the studies presented in the NDA and the follow-up long-term extensions demonstrate a large effect of Seroquel on weight gain. Based on the placebo-controlled studies using doses recommended for schizophrenia, as much as 90% of the weight gain in Seroquel-treated subjects was caused by the drug.

C.1.2. Glucose Abnormalities and Insulin Resistance in Response to Seroquel Treatment

Increased weight is a major risk factor for elevated glucose, hyperinsulinemia, and Type II diabetes mellitus. Glucose measures were collected in most studies and in every US study completed as part of the NDA. Clinically significant increased glucose was defined to be greater than 13.9 mmol/L or 250 mg/dl. However, limited data were provided in the NDA related to glucose, insulin, or other biochemical indices of metabolic risk.

Studies 126 and 127 were conducted with secondary aims to evaluate more detailed measures of glucose homeostasis. In these two trials, there were 5 cases of diabetes in the Seroquel group (n=646) compared to one in the placebo group (n=689). The difference between Seroquel- and placebo-treated patients was pronounced for glucose values > 200 mg (2.9% and 0.5%, respectively). Among Seroquel-treated subjects, 12.2% of them had at least one glucose value greater than 250 mg/dl compared to only 8.1% of placebo treated subjects. Analyses adjusted for length of follow up and restricted to participants who had fasted for at least 8 hours showed even greater treatment differences with respect to glucose. Seroquel patients had a greater mean increase (5.0 mg/dL) in glucose relative to participants randomized to placebo (-0.05 mg/dL). Elevated Hba1C (> 7.5), a longer term marker of glucose elevation, occurred in 2.1 vs. 0.8 percent of Seroquel versus placebo participants. In aggregate, these data clearly show the excess of glucose abnormalities in subjects randomized to Seroquel.

At the request of the Food and Drug Administration in May, 2000, Astra Zeneca evaluated disturbances in glucose regulation in their Phase I-III program as well as post-marketing surveillance. In the short-term (i.e., less than 6 weeks duration) placebo-controlled studies, only 230 Seroquel treated subjects and 143 placebo-treated subjects had glucose measurements analyzed, and Seroquel treated subjects had higher values of glucose than their placebo counterparts (3.6 (1.52 SE) vs. -0.26 (1.93), p=.12, respectively). Additionally, 3.4% of 323 Seroquel treated subjects

versus 0.7% of 143 placebo-treated subjects had a glucose value in excess of 200 mg/dl during the short term trials (relative risk 4.87, 95% confidence interval 0.83-29.30, p=0.116). In June, 2007, a clinical overview was conducted for the purpose of providing data to support changes to the Core Data Sheet. In that analysis, glucose, insulin, HOMA, and HbA1C were evaluated in the composite of studies that had been conducted. The data indicate that Seroquel is associated with metabolic abnormalities with respect to glucose, insulin resistance, and diabetes. Among the 11,013 Seroquel treated subjects, the mean increase in blood glucose was 0.2 (1.62) mmol/L compared to 0.059 (1.46) mmol/L in 1,592 placebo treated subjects. Differences were much larger for HOMA, a measure of insulin resistance that is sensitive to weight (i.e., subjects who gain weight become more insulin resistant): the difference in means was five fold greater for Seroquel versus placebo [1.26 (9.5) in 2265 Seroquel subjects versus 0.37 (10.83) in 640 placebo subjects]. Not unexpectedly, given these differences in glucose and insulin resistance, the relative risk for diabetes was 2.02 (p=0.49, 95% CI 0.31-12.04).

Since most of the participants in the randomized clinical trials were treated for a short period of time, the actual person-time contributed is small, and may have not yielded sufficient power to detect the excess risk of diabetes associated with Seroquel. However, as early as 1999, Dr. J. Small indicated in her draft for a book chapter for Psychopharmacology of Schizophrenia that "as...quetiapine cause the most weight gain, these drugs may be the most likely to induce diabetes." Once Seroquel was approved by the FDA and administered to large numbers of patients, there was early evidence of an increased risk of diabetes with Seroquel treatment. In 2003, Koller et al published a report using data derived from the FDA Medwatch, a surveillance program for spontaneously reported adverse events. During the period 1/1/97 through 8/15/02, they showed that Seroquel use unmasked or precipitated diabetes, the onset was rapid and severe, and removal of the drug resolved the condition in some cases.

Subsequent observational studies (cohort and case-control) confirmed the excess risk of diabetes with Seroquel. For example, Guo et al, using an integrated, seven-state, Medicaid-managed, care claims database from 1/1/98 through 12/31/02, reported the relative risk of diabetes was 2.5 (95% CI 1.4-4.3) in Seroquel users compared to users of conventional antipsychotics. Other studies have suggested that the diabetes risk increases with greater exposure time. For example, Dr. Lambert and colleagues reported from the Veteran's Affairs database that Seroquel was associated with an increased risk for diabetes compared to conventional antipsychotics (RR 1.67, 95% CI 1.01-2.76) and that the risk increased with greater treatment duration (RR for 52 weeks of treatment 1.82, 95% CI 1.32 – 2.49). Other studies have found relative risks for quetiapine versus conventional antipsychotics to range from 1.17 (95% CI 1.06 – 1.30; Ollendorf et al, 2004) to 3.15 (95% CI 1.63 – 6.09; Citrone et al, 2004), with other studies by Sernyak, Leslie, Lambert, and Guo showing relative risks between these two extremes (see Table 2). However, all studies used conventional treatment as the comparison group rather than non-treatment, which could result in a confounding effect, i.e., attenuation of the effect size of Seroquel, if these treatments also were causally related to diabetes. For example, compared to non-treatment,

Sacchetti et al reported a relative risk of 33.7 (95% CI 9.2 – 123.6) for Seroquel. Most studies reported also have a very limited time window of exposure and a small number of subjects exposed to Seroquel.

Table 2: Observational Studies reporting Relative Risks of Seroquel compared to Conventional Antipsychotic Treatments		
First Author	Year	Relative Risk (95% Confidence Interval))
Sernyak	2002	1.31 (1.11 - 1.55)
Citrone*	2004	3.15 (1.63 – 6.09)
Feldman*	2004	NR (1.3 – 2.9)
Ollendorf *	2004	1.17 (1.06 – 1.30)
Leslie*	2004	1.20 (0.99 – 1.44)
Lambert*	2005	1.2 (0.80 – 1.70)
Guo*	2005	1.8 (1.4 – 2.4)
Lambert*	2006	1.67 (1.01 – 2.76)
Guo*	2007	2.5 (1.4 – 4.3)
* indicates industry support among investigative team members, NR=not reported		

C.1.3. The Effect of Seroquel on Triglycerides and Cholesterol

Seroquel has consistent and detrimental effects on triglyceride values which is congruent with its effects on weight and glucose / insulin abnormalities. As stated in the Integrated Safety Report, clinically significant increased triglycerides were defined as a doubling of triglycerides above the upper limit of normal. In aggregate in the Phase II and III placebo-controlled studies summarized in the Integrated Safety Report, the relative risk for increased triglycerides above the normal range at the end of the treatment was 2.7 (22.3% of Seroquel users versus 8.2% of placebo users). The percentage of participants who had a clinically significantly high triglyceride value at any time during these studies was even greater in Seroquel versus placebo users (26.3% versus 8.2%). Cholesterol values showed a similar pattern.

D. Metabolic Derangements associated with Seroquel outweigh Benefits of Treatment

Given the totality of evidence regarding the increased metabolic risk with Seroquel treatment, the relative benefit of Seroquel compared to other antipsychotic agents is debatable. In fac, in 1997, Dr. L. Arvanitis questioned the competitive advantage of Seroquel. In her review of the data regarding weight gain, she stated "I was really struck by how consistent the data was across pools...across parameters / measures...across cohorts." In her summary, she stated that the weight gain was rapid but continued to increase with continued treatment and that the weight gain was 45% at 52 weeks of treatment. She concluded that she did not see a "competitive opportunity" no matter how weak. Subsequent studies confirmed Dr. Arvantis' concern that Seroquel's benefit / risk profile is not superior to other drugs in the class. In aggregate, the drop out rate in the Phase II and III studies was consistently highest

for Seroquel compared to haloperidol or chlorpromazine. The largest and most carefully done study to address the overall effectiveness across drugs in this class was conducted by the National Institutes of Health, specifically, the National Institute of Mental Health. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study randomized 1493 patients with schizophrenia at 57 U.S. sites to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months; ziprasidone (40 to 160 mg per day) was included after its FDA approval. The primary outcome measured used to define effectiveness was withdrawal from the study for any reason. That study found that the time to the discontinuation of treatment for any cause (i.e., the primary outcome measure) was longer in the olanzapine treated subjects than in the Seroquel treated subjects (hazard ratio, 0.63; $P<0.001$). Additionally, the time to the discontinuation of treatment for lack of efficacy was longer, and the total duration of successful treatment longer, in the olanzapine treated subjects than in the quetiapine treated subjects (hazard ratio, 0.41; $P<0.001$ and 0.53; $P<0.001$, respectively). Finally, another indicator of poorer efficacy is the proportion of patients who take the maximal dose of a drug: a higher proportion of patients assigned to quetiapine received the maximal dose allowed in the study.

E. Astra Zeneca Failed to Warn Future Patients and Physicians about the Metabolic Risk associated with Seroquel

Despite the consistent clinically and statistically significant increases in weight and other metabolic parameters noted in all Phase II and III studies presented in the Integrated Safety Report, none of the weight or metabolic factors were listed in the summary of the risks and benefits provided at the conclusion of that report. Publications of the Phase II and III studies never mentioned increased weight or other metabolic abnormalities in the abstract of the publication (i.e., the summary of a scientific publication that is publicly available through various search engines such as PubMed). Within publications, the weight data were listed at the end of results sections, and in the discussion section, dismissed as expected complication of treatment.

F. Astra Zeneca Promoted Seroquel as Metabolically Neutral

Early publications of Seroquel Phase II and III randomized clinical studies promoted Seroquel as metabolically safe despite the large, consistent, and statistically significant findings of weight gain, reduced T4, and hypertriglyceridemia in the clinical trials included in the NDA application in 1996. Even as late as 5/22/99, Astra Zeneca produced a news release from the APA meeting in Washington stating Seroquel "reduces weight gain" and that the "potential to gain weight and develop diabetes.....can be minimized with Seroquel." This data --- for which a news release was created --- were based on retrospective chart review of a case series of 60 patients. This design is the weakest of all designs in epidemiologic research, and the results from this study were in sharp contrast to the totality of evidence from the gold

standard of research designs, namely, the placebo-controlled randomized clinical trials that comprised much of the data submitted with the NDA.

In 2000, publications supported by the company by Breecher et al; describe Seroquel as having a 'favorable weight profile", consistent with the "recommended vocabulary". In 2003, Seroquel's management team created "key messages" to be used in publication. And again, Seroquel's "favorable weight profile" was a key message of Astra Zeneca. In February, 2005, a document created by Astra Zeneca entitled "Seroquel Vocabulary and Descriptors Summary Document" was finalized. Its purpose was to communicate accepted vocabulary to be used in all publications from Seroquel as well as language to be avoided or not used. With respect to weight, the "recommended" vocabulary to be used in publications was "favorable weight profile" and "minimal weight gain". For diabetes, recommended statements generally highlighted either the increased risk of diabetes in schizophrenic patients or the weaknesses of epidemiological studies and confounding as likely reasons of excess diabetes risk associated with Seroquel treatment. In 2006, the Division of Drug Marketing, Advertising, and Communications of the U.S. Food and Drug Administration ordered Astra Zeneca to "cease the dissemination of violative promotional materials for Seroquel" because of false or misleading statements that minimized the risk of hyperglycemia and diabetes mellitus.

In aggregate, this brief and non-exhaustive list of examples point to a concerted effort to promote Seroquel as safe and metabolically neutral in the context of compelling placebo and active comparator controlled clinical trials indicating the drug was associated with substantial metabolic risk.

G. Astra Zeneca withheld Support for Studies Regarding Seroquel's Metabolic Risk

Astra Zeneca consistently withheld support for studies which could demonstrate Seroquel's lack of safety relative to other antipsychotic agents. As evidenced by an email from Dr. Goldstein, July 18, 2002, an investigator requesting 3 grams of Seroquel to study diabetogenic and hyperlipidemia side effects of Seroquel and other atypical antipsychotics was denied by Astra Zeneca. Dr. Goldstein stated "This would be an interesting study but carries substantial risks that we do not differentiate from olanzapine or clozapine. This would be damaging.....I would not want to enter into a study that could provide any data that could influence regulatory authorities against us." Additional internal communications from Dr. Goldstein reinforce the stance of Astra Zeneca with regard to initiating studies. For example, Dr. Goldstein states in another email "they don't want to introduce studies that could potentially damage Seroquel's comparison against other atypical's."

In 2005, Astra Zeneca promoted a policy that gave "green" or "red lights" to make funding decisions for research proposals brought forward from independent investigators. A "red light" was given for glucose and/or metabolism investigator sponsored studies. Specifically, Astra Zeneca's stated policy for glucose or metabolism studies was "don't bother for red". In light of the totality of data within

their own studies indicating the metabolic derangements associated with Seroquel treatment, and subsequent observational epidemiological studies indicating the diabetes risk associated with treatment, this was an unreasonable approach with respect of patient safety.

As medical literature is consistently being published and new evidence from other sources is emerging in reference to this subject I reserve the right to supplement this

I have participated in two trials involving Vioxx.

Donna K. Arnett

Donna K. Arnett, Ph.D., M.S.P.H.

Who's Who at AstraZeneca

Witness	Position/Background
Aked, Dominic	Medical Affairs Manager
Arnold, Barry, MD	EU Qualified Person for Pharmacovigilance (January 2006 to present); VP Clinical Drug Safety (July 1999 – May 2006)
Arvanitis, Lisa	Former Seroquel Project Physician
Basma, Alie	Safety surveillance team member
Beamish, Don	Commercial Brand Executive Director
Birkett, Geoffrey	Former Vice-President Global Marketing
Bowen, Rebecca	Marketing
Brecher, Martin, MD, MBA	Former Medical Science Director
Brennan, David	Chief Executive Officer, Chairman of the Senior Executive Team, Former Senior Vice-President for Commercialization and Portfolio Management, and former Chairman of the Operations & Portfolio Management Team
Campbell, Denise	Consumer Brand Director
Daniels, Stephanie	Medical Publications
Davis, Chester	State Government Affairs Director
Dev, Vikram	VP, U.S. Drug Safety (June 2006 to present); Senior Medical Director (1999-2004)
Fors, Susanne	Global Regulatory Affairs Director
Gaskill, James	Director Promotional Regulatory Affairs
Geller, Wayne, MD	Medical Director, Drug Safety and former Global Drug Safety Physician (GDSP) for Seroquel
Giddens, Russell	Head of Global Regulatory Affairs for Seroquel
Goldstein, Jeffrey, Ph.D.	Former Director of Clinical Science
Greenidge, Edmund	Promotional Regulatory Affairs
Haas, Ed	Pharmacologist at AZ
Hamill, Kevin	Brand Manager, HCP Primary Care
Holdsworth, Debbie	Commercial
Jackson, Marianne	National Sales Director
Jones, Martin	Global Product Statistician
Lawrence, Richard	Commercial Strategist
Leong, Ronald	Senior Medical Director
Limp, Gerald	U.S. Regulatory Affairs
Lloyd-Washington, Lisa	Seroquel Brand Director
MacFadden, Wayne	Former Director Clinical Research and U.S. Physician for SSeroquel
McKenna, Kevin	VP, Regulatory Affairs, Neuroscience Therapeutic Area
Melville, Margaret	Senior Global Regulatory Affairs Director
Minnick, Jim	U.S. Public Relations
Meulien, Didier	Psychiatrist on the Seroquel Team
Mullen, Jamie	Senior Director, Clinical Research

Witness	Position/Background
O'Brian, Shawn	Commercial
Oldham, Alex	Global Product Team Director
Owen, Richard	Medical Affairs Manager
Patterson, John	Former Executive Director, AstraZeneca PLC (Jan. 2005 to present); Executive VP, AstraZeneca PLC (Jan. 1999 – Dec. 2004)
Post, Janet	Seroquel Study Physician
Rak, Ihor	Seroquel Team Physician in Neuroscience
Repp, Ed	Seroquel Brand Communication Director
Ruhl, Athena	Seroquel Senior Product Manager
Schwartz, Jack	Executive Director, Seroquel Development
Shaw, Joan	Clinical Project Director for Seroquel
Spiers, Janet	Drug Safety Specialist and Safety Evaluation Review Meeting (SERM) Manager
Travers, John	Psychiatrist
Tumas, John	Chair of Seroquel Publications Team
Warner, Linda	Drug Safety Surveillance Associate Director (August 2004 to present); Drug Safety Surveillance Team Leader (May 2002 – July 2004)
Westhead, Emma	Statistician or medical writer
Williams-Hughes, Celeste	Medical Communications Specialist
Zook, Anthony	President and CEO of AstraZeneca US (2006 to present); Senior VP, Commercial Operations (2001-2006); VP Marketing & Sales (1997-2001)