From: Melville, Margaret G
Sent: Friday, May 24, 2002 12:43 PM
To: Izuishi, Koji; Mitani, Michiyo; Nakajo, Hirochika
Cc: Oldham, Alex; Brecher, Martin; Geller, Wayne; Fitton, Lesley R; Bowen, Rebecca; Schwartz, Jack A; Sawai, Etsuko; Trumble, Sharon M; Lapp, Carrie
Subject: Seroquel Hyperglycaemia -- proposed responses to MHLW -- Global Product Team comment to many issues!

Attachments: 0041summary.doc; 0043summary.doc

Dear Izuishi-san, Mitani-san, Nakajo-san,

Our glucose document may of course be submitted to MHLW. We have also looked into the availability of other information. We have received replies from Richard Owen and Jeff Goldstein regarding the pharmacology of quetiapine as it relates to weight gain. There is nothing of a strictly pharmacological character to tell the MHLW. We can note the differential effects on body weight and can cite the article below which demonstrates impaired glucose metabolism with olanzapine and clozapine.

Evidence for insulin resistance in patients treated with clozapine or olanzapine (independent of differences in adiposity) were found by Newcomer et al (Arch Gen Psychiatry 2002; 59 (4):337-345). The exact cause of the insulin resistance is not known. It could be due to e.g. alterations in insulin receptor kinetics and signaling mechanisms or decreases in the number or half-life of insulin-sensitive glucose transporters.

I know that you and Nakajo-san have questions about the history of glucose/diabetes worldwide, so I have provided you an update below.

Glucose/Diabetes WorldWide Labelling History

As you know diabetes mellitus is listed in the US PI. This was done at the time of approval. On 1 May 2000, the FDA did send us a letter requesting information pertaining to this broad issue. Informally, they informed us that they were considering sending a letter to Lilly requesting a higher level of labeling precaution for diabetes for Zyprexa, but first wanted to see whether the other drugs in this atypical class also had a similar problem (might justify a class label precaution, in other words), and so, we assume Janssen received a similar letter.

Specifically, the FDA's letter requested more extensive safety information regarding new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis. AZ sent a response dated 31 August 2000. No labelling changes have been required.

The issue of glucose and diabetes for risperidone, clozapine, and quetiapine (anti-psychotic medications) was reviewed by the Pharmacovigilance Working Party of the EU CPMP (see attached) in June 2001. The following was the suggested language for Seroquel. The MEB, the Dutch Health Authority and the RMS for the MR territories, agreed with the language and asked that this be imposed.

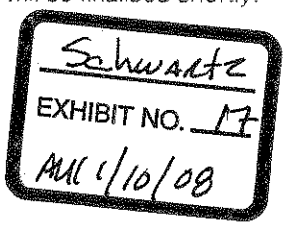
Section 4.4 Special Warnings and Precautions for Use

Hyperglycaemia or exacerbation of pre-eisting diabetes has been reported in very reare cases during quetiapine/Seroquel treatment. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Section 4.8 Undesirable Effects

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also Section 4.4 Special Warnings and Precautions for Use).

We sent in a review of our in house data at that time, but the MEB insisted on the change. We agreed to amend the SmPC in a Type II variation in November of 2001 with the above wording and this will be finalised shortly.



In February 2002 we received requests to change the SmPCs for Italy, UK, and New Zealand. In Italy we have agreed to adopt the language because the language already exists in the labels of competitors so we felt it was unacceptable to argue our case.

The UK have attempted to defend not adding the language to the SmPC at this time, and have sent in the previous glucose document (originally submitted to MEB) with a recent data cutoff. It is the document you will send to MHLW. They have stated that we are awaiting data from Study 0041, which has fasted glucose levels, and will review the situation then.

New Zealand's Health Authority MedSafe had asked that we adopt different language to that agreed above. We therefore submitted the new glucose document to New Zealand. MedSafe have responded with new suggested wording, and we have reluctantly agreed, changing the MedSafe Wording to the following. It is likely this will be agreed in the next months.

Hyperglycaemia, diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis, have occurred **very** rarely with quetiapine therapy. The causal association with quetiapine has not been established.

Then, I also wanted to provide you HQ thoughts on the proposed amending of the JPI. We are also very pleased that you have agreed not to file a JPI amendment at the time you provide the follow-up to MHLW on the diabetic coma death. In discussions in our team, we would like to propose the following plan:

- supply follow up to initial AE report, glucose document, any mechanistic arguments (if we have anything further) on May 28. Advise MHLW that we are currently reviewing and discussing the situation, and considering the JPI wording. Clearly discern ourselves from olanzapine. Glucose document, other AE tables already sent in, will support this belief.
- confer with MHLW over the information. At this point it is likely we will need to send an amended JPI in.
- provide new wording, below, at that time:

Significant side effects
Hyperglycaemia: Hyperglycaemia may **rarely** appear. Observation should be fully carried out. If any abnormalities are found, administration should be stopped **if other causes of hyperglycemia have not been found**, and appropriate action such as administration of insulin preparations should be taken.

- If MHLW does not agree to this wording suggest the following. We do not agree that wording such as olazapine has now in the JPI is appropriate for Seroquel.

Careful administration (The drug should be given with particular caution in the following patients. Patients with diabetes or a history of diabetes

Significant side effects
Hyperglycaemia: Hyperglycaemia may **rarely** appear. Observation should be fully carried out. If any abnormalities are found, administration should be stopped **if other causes of hyperglycemia have not been found**, and appropriate action such as administration of insulin preparations should be taken.

Should you still require data on Patient's exposure in Japan, I have copied Carrie Lapp on this. Carrie -- the issue is below:

In response to your question below, it is possible to calculate the number of patient-years exposure provided that you supply the average dose per patient per day, however the more meaningful estimated number of patients exposed would be preferred. In the US, models have been constructed based in part upon the average number of prescriptions filled per unit time per patient. I will copy Chris Maurer from the US on this to see what else is needed in calculating the number of patients exposed to Seroquel in Japan.

Chris responded that he did not have numbers for Japan. Do you Carrie?

As for what fasting blood glucose data we will have, we have expected to have data in late 3Q2002 from Study 0041. We are also expecting information from Study 0043 in 4Q02 or 1Q03. The protocol summaries are enclosed below.

0041summary.doc
(29 KB)

0043summary.doc
(30 KB)

I am sorry that this is such a long email with so many things in it. Should you have any questions or clarifications, please do not hesitate to let me know. As I am going to be in Europe next week, I will not be so far behind you in time. I also will be available from Monday May 27 late am by email.

Best Regards,

Margaret (Meg) Melville
Seroquel Global Regulatory Affairs Director
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-----Original Message-----
From: Izuishi, Koji
Sent: Wednesday, May 22, 2002 9:09 PM
To: Melville, Margaret G
Cc: Oldham, Alex; Brecher, Martin
Subject: RE: Seroquel and hyperglycaemia

Dear Margaret-san

I'd like to confirm may I submit 'your glucose document' to MHLW at the hearing?
I also want to know that this document was submitted NZ authority, was it requirement form the authority?
If so why the authority required such information?

If you know above three question, please let me know.

By the way we will go to hearing next Monday or Tuesday. AZKK team will discuss the methods that how to negotiate the MHLW at Friday lunchtime . If you have any other useful information as differentiation between seroquel and olnazapin et.al, please let me know ASAP.

Regards
K.Izuishi (ex3819)
AstraZeneca K.K

-----Original Message-----
From: Izuishi, Koji
Sent: Tuesday, May 21, 2002 6:28 PM
To: Melville, Margaret G
Cc: Oldham, Alex
Subject: RE: Seroquel and hyperglycaemia

Dear Margaret-san

Thank for your prompt reply and kindly hospitality during my visit.

This assessment report looks very useful document to discuss JPI issues with MHLW.
Therefore is it possible to submit this document to the MHLW at the hearing ?
If it is Ok, it makes more strong negotiation to them.
Please let me know acceptability to submit.

Regards

K.Izuishi (ex3819)

AstraZeneca K.K

-----Original Message-----
From: Melville, Margaret G
Sent: Saturday, May 18, 2002 6:08 AM
To: Izuishi, Koji; Geller, Wayne; Brecher, Martin; Mitani, Michiyo
Cc: Fitton, Lesley R; Bowen, Rebecca; ; Trumble, Sharon M
Subject: FW: Seroquel and hyperglycaemia

Dear Izuishi-san, Ali,

As we have discussed, as we are all together in Baltimore, this document, recently prepared for Health Authorities requests, may be useful to you in your preparations to respond to MHLW on May 28. It is a recent review of glucose/diabetes from both a clinical and postmarketing perspective.

Wayne, Martin and I will see you tomorrow night in Philadelphia and can update you then.

Best Regards,

Margaret (Meg) Melville
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-----Original Message-----
From: Trumble, Sharon M
Sent: Monday, April 22, 2002 10:05 AM
To: Carbines, Michelle
Cc: Melville, Margaret G
Subject: RE: Seroquel and hyperglycaemia

Dear Michelle,

Please find attached the glucose document to defend the issue of Seroquel and hyperglycaemia with the New Zealand HA, I apologise for the delay.

<< File: Glucose Diabetes.pdf >>
Could you please send me a copy of your response/defence letter when you submit this documentation to the NZ HA.

Please let me know if you require any additional information

Kind regards
Sharon

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

From: Carbines, Michelle
Sent: 10 April 2002 06:02
To: Melville, Margaret G; Trumble, Sharon M
Subject: Seroquel and hyperglycaemia

Hi Meg and Sharon

Just following up on the hyperglycaemia issue as we advised Medsafe that we would have a response to them by mid April which is nearly upon us. Are we still on track?

Thanks and kind regards
Michelle.

Michelle Carbines
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