Unknown

From: Melville, Margaret G
Sent: den 23 oktober 2002 17:29
To: Mitani, Michiyo; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Schwartz, Jack A; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki; Warner, Linda (Safety); Jonsson, Marianne
Subject: GPT delay in commenting to MHLW proposed JPI wording

Dear Mitani-san,

It sounds that you had a hard meeting with the MHLW. I think the good points are that there is no Dear Dr. Letter and nothing in Contraindications (unlike olanzipine).

I am very, very sorry, but the team was not present to accept your language today. We must ask that you accept that you will get it on October 24 late your day. I hope that you understand but since it is very different from what we proposed I feel I must get agreement from the team. We will commit however, to respond to your proposal on October 24 US day and you will then have this for October 25 Japan day.

I will also respond tomorrow on whether it is o.k. as you have proposed to have you amend the JPI with no further GPT comments.

Again, I apologise very much for not responding sooner. I hope you know that I do understand your urgency.

Best Regards,

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

From: Mitani, Michiyo
Sent: Wednesday, October 23, 2002 9:49 AM
To: Melville, Margaret G; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki; Warner, Linda (Safety); Jonsson, Marianne
Subject: RE: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear All,

We had an interview with MHLW today.

MHLW considers that prompt PI revision (as information to medical institutions) is essential. It should differ from ordinary PI revision procedures. The reason is the hyperglycaemic issue became significant with olanzapine, and MHLW has been watching this issue with special attention.

At the interview AZKK PI revision draft was instructed to be rewritten to include following instructions to be submitted by 25 Oct. MHLW requested our prompt action as severe as Dear Doctor Letter. (Of course, Dear Doctor Letter was not instructed.) MHLW plans to have examination meeting within Safety Division in early next week and to deliver the revised PI information to medical institutions in the week after next.

MHLW Comments on AZKK draft:
[Clinically Significant Adverse Reactions]

Schwartz
EXHIBIT NO. 22
MK 4/10/08

1. If "exacerbation of pre-existing diabetes mellitus" is included, it can be read that the ADR may occur only in patients having diabetes mellitus. When "hyperglycemia" and "diabetic ketoacidosis" are listed, "exacerbation of pre-existing diabetes mellitus" can be considered well expected from these events. Therefore, "exacerbation of pre-existing diabetes mellitus" should be deleted.

2. The word "rarely" is not appropriate.

3. Management in case of development of these events should be included.

[Important Precautions]
1. It was considered inappropriate to include the text restricting patients to those having diabetic risk factors. - - - At first they commented so, but examining the reported cases, their comment changed that it is uncertain whether the hyperglycaemia may occur in patients who do not have diabetes mellitus or diabetic risk factors, and they began wavering whether it is acceptable to restrict patients to those having diabetic risk factors or not.

2. Since "PET bottle syndrome" is not an authorized medical term, it is inappropriate to include it in PI.

3. The text "A causal relationship with Seroquel has not bee established." should not be included in "Precautions for Use" section.

[Careful Administration]
1. The event should be included in "Careful Administration" section as well as in "Clinically Significant Adverse Reactions" and "Important Precautions" sections.

2. The patients requiring careful administration are: patients with diabetes mellitus, having past diabetic history, and having diabetic risk factors.

According to the above instruction, we have revised the PI text again.

Because we are in the condition requiring our action as severe as Dear Doctor Letter, we have to revise the PI to reflect all of the above instructions. We have to submit our revised draft to MHLW by 25 Oct. Would you please accept our revised wording as below. Until the PI text is fixed, MHLW may give small additional instructions, but the time to be given to us is too little to examine them. It would be appreciated if you approve us to fix the final JPI text at our discretion.

AZKK revised draft
[Clinically Significant Adverse Reactions]
Hyperglycaemia, diabetic ketoacidosis (frequency unknown)
Hyperglycaemia and diabetic ketoacidosis may occur. Therefore, patients should be carefully monitored, and if any abnormality is observed, appropriate measures such as discontinuation of the drug should be taken.

[Important Precautions]

- We will try to submit the text restricting patients, and if MHLW does not accept it, the alternative text will be submitted. -

1. text restricting patients
In patients having hyperglycemia or risk factors such as obesity, Seroquel may increase blood sugar level and rapidly aggravate metabolism disorder. In such patients, symptoms such as thirst, excessive drinking, polyuria and urinary frequency should be carefully monitored, and blood sugar level should be analysed if necessary during treatment with Seroquel.

2. (alternate) text not restricting patients
Seroquel may increase blood sugar level. Symptoms such as thirst, excessive drinking, polyuria and urinary frequency should be carefully monitored, and blood sugar level should be analysed, if necessary during treatment with Seroquel.

[Careful Administration]
Patients with diabetes mellitus, having past diabetic history, having diabetic risk factors such as family history of diabetes, hyperglycemia and obesity. (See "Important Precautions" section.)

It would be appreciated if you would send your reply approving the above wording to reach us by 24 Oct (Japan

time).

Thank you very much for your help.

Kind regards,
Michiyo

-----Original Message-----
From: Melville, Margaret G
Sent: Wednesday, October 16, 2002 7:05 PM
To: Mitani, Michiyo; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki; Warner, Linda (Safety); Jonsson, Marianne
Subject: RE: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear Mitani-san,

Thank you so much for your note. Thank you also for your decision to tell Fujisawa to use our wording. We were worried this would happen and I'm sure you agree that it would be good in future if there is time that we communicate to each other before Fujisawa.

REDACTED

And thank you again Mitani-san and your team for your understanding of our issues.

Best Regards,

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-----Original Message-----
From: Mitani, Michiyo
Sent: Wednesday, October 16, 2002 4:12 AM
To: Melville, Margaret G; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki; Warner, Linda (Safety); Jonsson, Marianne
Subject: RE: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear Melville-san,

Thank you very much for your understanding of Japanese condition. And thank you very much again for the "Assessment of Diabetes in Patients Treated with Seroquel: Response to Japanese MHLW", it was so marvelous.

We agree that the wording in "Clinically Significant Adverse Reactions" section which you recommended in red letters.

In yesterday's discussion with Fujisawa, they proposed draft different from ours. Its language was severer than AZ draft. Fujisawa draft was examined in AZKK, and we have concluded to tell Fujisawa to go on the JPI revision using AZ draft. If such decision causes any problem, we will inform it to you.

Kind regards,
Michiyo

-----Original Message-----
From: Melville, Margaret G
Sent: Wednesday, October 16, 2002 7:19 AM
To: Mitani, Michiyo; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki; Warner, Linda (Safety); Jonsson, Marianne
Subject: RE: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear Mitani-san, All,

Thank you so very much for your reply.

I understand completely why you cannot add the causal association statement to the Adverse Event Section of the label. It is o.k. to remove it from this section alone. We then recommend that you amend the wording instead to read:

"Hyperglycaemia, exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis (frequency unknown): Hyperglycaemia, exacerbation of pre-existing diabetes mellitus and diabetic ketoacidosis have been observed rarely."

The other language implies that there may be some causality or mechanistic rationale for expecting these events, as if we know that it may occur rarely. Our new language simply states that these things have been observed.

But keeping the causality statement out of the AE section is fine, as it is more important that it be in the precautions section. We appreciate that you will negotiate the causal sentence in precaution with MHLW, particularly in light of your other discussions on another product. We find it imperative to attempt with MHLW to add this to the JPI.

We do not believe a VC is necessary. Considering how late in the evening you would have to attend, and that we agree, there is no need. Thank you so much for offering.

Sharon Trumble will give you the information you require on the SPCs -- we have wording agreed with the Italy HA but no new SPC, and she will pass that, and the EU MR SPC, which has not changed and was already approved, to you.

Please also find the document promised below entitled "Assessment of Diabetes in Patients Treated with Seroquel: Response to Japanese MHLW." We owe Linda Warner and Ron Leong a big thank you for producing this good report so quickly. Our view is that it supports the proposed JPI language very well.

As I understand it, the discussions with Fujisawa were today. It is our sincere hope they were in agreement with the proposed JPI attached. Can you confirm that Fujisawa were in agreement? And I also know you will keep us informed what happens with MHLW next week.

I have saved the most important part for last. I am so sorry that we did not meet with Kimura-san!! It was our intention -- in fact, we set up a meeting at 8 am for today, October 15. However, the person who arranged the meeting thought that I would inform Kimura-san, and I thought the person setting up the meeting would tell Kimura-san. It was my horrible mistake. We very much wanted to talk to Kimura-san on this issue. Instead, he left on the plane. Kimura-san, will you accept my apology?

Best Regards,
<< Message: Seroquel/Diabetes/ Japan >>

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

From: Mitani, Michiyo
Sent: Tuesday, October 15, 2002 6:15 AM
To: Melville, Margaret G; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki
Subject: RE: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear Melville-san,

We have discussed the wording of revised JPI within AZKK according to your comment.
Please find the attached Seroquel JPI including these revised texts in red letters.
<< File: Seropuel PI-E_021015draft.doc >>
Concerning the wording in "Important Precautions" section, we plan to negotiate the recommended wording with MHLW. However, would you accept our draft of the clauses in "Clinically Significant Adverse Reactions" section.

According to the rules of description of "Precautions for Use"of JPI, it is uncommon to add the provision "A causal relationship with Seroquel has not been established" in both sections. It is scarcely possible that MHLW accepts to add such sentence. Espeically in "Clinically Significant Adverse Reactions" section, all ADRs, of which causal relationship with the drug cannot be denied, should be included without distinction regardless of the establishment of causal relationship. Therefore, it is impossible to add the sentence. If we submit our revised JPI draft including the sentence to MHLW, the sentence may make the official displeased, and negotiation of the revision would become difficult. Recently our negotiation of JPI revision of other product has displeased an MHLW official, so, if Seroquel JPI revision would also make them displeased, our future negotiation of other products concerning JPI will be further difficult.

We're going to negotiate the wording of the "Important Precautions" section as you recommended, so would you please accept the wording of "Clinically Significant Adverse Reactions" section without the sentence "A causal relationship with Seroquel has not been established". It is possible that MHLW may instruct us to delete the sentence even from the text of "Important Precautions" section, and the order of the items in each section may change. Please accept such revision.

If additional discussion is necessary for the wording of these sections, we would like to have VC with you. We have booked our VC 28-2 from Japan time 21:00 (US time 8:00 a.m.) of 16 Oct. Izuishi-san, Ose-san, Sawai-san and I will attend the conference, and if possible, Kimura-san will. If you think the discussion is necessary, please inform us within today.

In this morning, I talked with Kimura-san who was in Wilmington on the phone. He did not see your e-mail reply. He had asked Piet to have contact with you, but he was told no one was there, so he thought that meeting was impossible. He told me that it was unfortunate, while he had expected to have communication from you or other Seroquel people, since both you and he were in Wilmington.

I would like to apologize you that we sent AZKK draft to Fujisawa before we obtained agreement within AZ. Fujisawa strongly requested us to send them revised JPI draft promptly, since Fujisawa in-house discussion was planned in 15 Oct. We sent our draft telling that the draft is not agreed by AZ HQ, since prompt action was necessary. We have not yet confirmed result of the Fujisawa discussion. We will tell it to you as soon as we obtain it.

Would you confirm whether the document prepared by Drug Safety entitled "Assessment of Diabetes in Patients Treated with Seroquel: Response to Japanese MHLW" has been finalised or not. If the document is finalised, please send it promptly.

Is the wording of SPCs of Italy and EU MR unchanged from the previous version including EMEA recommendation in 2001? When were the SPCs revised? Was the revision issued? If the answer is yes, please send us the revised SPCs.

Kind regards,
Michiyo

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

From: Melville, Margaret G
Sent: Tuesday, October 15, 2002 5:45 AM
To: Mitani, Michiyo; Brecher, Martin; Leong, Ronald; Bowen, Rebecca
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki
Subject: GPT review of proposed Seroquel wording and answers to various queries for MHLW next week

Dear Mitani-san,

In preparation for your meeting at MHLW next week (October 21) we have just reviewed the document prepared by Drug Safety entitled "Assessment of Diabetes in Patients Treated with Seroquel: Response to Japanese MHLW". Preclinical, clinical, literature, and postmarketing data were reviewed. Cumulatively, there were 92 cases total, 13 Japanese cases (one other case was identified). The conclusions from this report are that:

Through 31 July 2002, there have been an estimated four million Seroquel patient exposures worldwide. While there have been a relatively small number of postmarketing reports of glucose dysregulation in patients using Seroquel, there is currently inconclusive evidence to suggest that Seroquel negatively influences glucose regulation causing new-onset diabetes mellitus or worsening of preexisting diabetes mellitus. Following a careful review of all diabetes related reports received from both Japan and all other countries, it was determined that assessment of causality was difficult in these cases because of either scant clinical detail, unclear temporal sequence of exposure and outcome, or confounding by concomitant medications and illnesses. Following a review of all the available relevant pre-clinical, clinical and safety information, as well as the medical/scientific literature, it was determined there is insufficient evidence to establish a causal relationship between Seroquel and glucose disorders.

Therefore, it is concluded that that no changes to the Seroquel core data sheet are indicated at this time. AstraZeneca will continue to keep reports of diabetes mellitus and related disorders under careful review."

You will receive this report shortly; it is being finalised right now.

Therefore, the draft language (below) you have supplied to us and Fujisawa is unsupportable.

[Important Precautions]
(4) In patients having hyperglycemia or diabetic risk factors including obesity and bulimia/excessive drinking (PET bottle syndrome* etc), etc, Seroquel may **increase blood sugar level and rapidly aggravate metabolism disorder**. In such patients, symptoms such as thirst, excessive drinking, polyuria and urinary frequency should be carefully monitored, and blood sugar level should be analysed if necessary during treatment with Seroquel.

[Clinically Significant Adverse Reactions]
3) **Hyperglycaemia, exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis** (frequency unknown)
Hyperglycaemia, exacerbation of pre-existing diabetes mellitus and diabetic ketoacidosis may rarely occur.

*: "PET bottle syndrome" was named after people habitually drinking large amount of sweet soft drinks

in 1 or 2 Litre of "PET plastic bottle".

Having reviewed your language and the document we strongly recommend the language below. This is consistent with changes made in other territories and includes a statement that there is no causal association between these events and Seroquel. This sentence is imperative; it is also the reason that the CDS does not need amending at this time. **We understand you are meeting with Fujisawa on October 14 and we recommend that this language be agreed with them.**

[Important Precautions]
(4) In patients having hyperglycaemia or diabetic risk factors including obesity and bulimia/excessive drinking (PET bottle syndrome* etc), etc, who have received Seroquel, **increased blood sugar level and rapidly aggravated metabolism disorder have been observed**. A causal relationship with Seroquel has not been established. In such patients, symptoms such as thirst, excessive drinking, polyuria and urinary frequency should be carefully monitored, and blood sugar level should be analysed if necessary during treatment with Seroquel.

[Clinically Significant Adverse Reactions]
3) **Hyperglycaemia, exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis** (frequency unknown)
Hyperglycaemia, exacerbation of pre-existing diabetes mellitus and diabetic ketoacidosis may rarely occur. A causal relationship has not been established.

*: "PET bottle syndrome" was named after people habitually drinking large amount of sweet soft drinks in 1 or 2 Litre of "PET plastic bottle".

In addition we were surprised that this language was sent to Fujisawa before being agreed within AstraZeneca. We understand the very tight and urgent timeframes you are working to but feel that having agreement internally before confirming with Fujisawa must be the way we work. Can you confirm that this is the way we will work until the license is transferred in February 2003?

After you have agreed this language with Fujisawa we would like to sign-off on the JPI change, but it would be best for us to see the whole JPI with the changes enclosed. We are fairly certain where you are going to place the sentences but forwarding the whole JPI would allow us the most thorough review. We assume you must supply something quickly (by end of the week?) and we will commit to reviewing rapidly.

With regard to your question regarding the status of any changed PIs I can confirm that the EU MR, New Zealand, Italy SPCs are all agreed with the Health Authorities. The US PI has not changed with regard to diabetes mellitus and UK label does not include any information regarding these issues. The MCA expect to review next month. Is this the information you require?

Finally, since these issues may arise over the next several months and due to time differences it is difficult to communicate is it possible that one member of your team can be a point-person and have a mobile telephone or another avenue of communication so that we can speak directly if it is necessary?

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-----Original Message-----
From: Mitani, Michiyo
Sent: Friday, October 11, 2002 3:26 AM

To: Melville, Margaret G; Brecher, Martin; Leong, Ronald
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Bowen, Rebecca; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki
Subject: RE: Safety Division (MHLW) Instruction on Seroquel JPI concerning Diabetes Mellitus

Dear All,

I have another request. Would you update "Glucose/Diabetes WorldWide History" which was informed to us in your mail of 25 May (please see the attached mail). MHLW often asks us whether PI in other countries has been revised or not. You told me that the wording was agreed by New Zealand MedSafe authorities. Are there any PI revisions in other countries?

<< Message: Seroquel Hyperglycaemia — proposed responses to MHLW — Global Product Team comment to many issues! >>

Thank you very much for your kind help.

Kind regards,
Michiyo

-----Original Message-----
From: Mitani, Michiyo
Sent: Thursday, October 10, 2002 6:17 PM
To: Melville, Margaret G; Brecher, Martin; Leong, Ronald
Cc: Izuishi, Koji; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Bowen, Rebecca; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko; Kimura, Satoru; Uechi, Yasuyuki
Subject: RE: Safety Division (MHLW) Instruction on Seroquel JPI concerning Diabetes Mellitus

Dear All,

Sorry for the delay of my reply.

As you may aware, we think that we should provide new wording to MHLW.

Izuishi-san, Togashi-san, Kimura-san and medical advisor had in-house discussion on the wording yesterday. According to the discussion outcome, we would like to propose the revised JPI wording as per attachment. We examined PI text of olanzapine, and concluded that we should make up our mind to revise the JPI text as strict as the attached one, or MHLW may impose us severer actions. So, would you examine our proposal positively.

<< File: SER hyperglycemia - Precautions for Use1.doc >>

This JPI revision draft has been sent to Fujisawa, today. The wording will be discussed at Fujisawa on 15 Oct.

We must submit the JPI revision draft including new wording to MHLW as soon as possible. After we obtain the discussion outcome from Fujisawa and GDSP case review from you, we plan to visit MHLW in the week from 21 Oct. PSUR is to be separately submitted to MHLW around 29 Oct.

I assume the attached wording may be controversial at your end. Kimura-san will visit Wilmington next week, so would you tell him your comments on this issue.

Position on trial 0041 is planned to be reported to MHLW after the result is obtained, while it may be late for our MHLW visit in the week of 21 Oct.

Thank you very much for your kind help.

Kind regards,
Michiyo

-----Original Message-----
From: Melville, Margaret G
Sent: Friday, October 04, 2002 7:34 AM
To: Izuishi, Koji; Mitani, Michiyo; Brecher, Martin; Leong, Ronald
Cc: Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Bowen, Rebecca; Street, Paul R; Ose, Kazuyuki; Trumble, Sharon M; Schwartz, Jack A; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko
Subject: RE: Safety Division (MHLW) Instruction on Seroquel JPI concerning Diabetes Mellitus

Dear All,

Please excuse my delay in replying. This issue is important to all of us.

Ron Leong, our new Drug Safety Physician, is now reviewing the cases you have provided below. We plan to provide our analysis, of both Japanese and Rest of World Cases, to you as you requested, on October 14. We have just completed a PSUR. Can I confirm that you would not be submitting this document as your timeframes for submitting are different?

Can I also confirm that you believe that we should provide new wording to MHLW? It appears this is necessary. If this is so then we will provide this as well on October 14. At this time, the wording agreed with the New Zealand MedSafe authorities may be best, since there is a statement on causal association:

"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."

I will discuss with Martin whether a position on Trial 0041 can be available for the end of October. I understand this would help you.

I will also discuss with Ron and Martin your question regarding the CDS. However, the company position is that there is no causal association between these events and Seroquel. As only events with a causal association are added to the CDS, there are no plans to have a CDS change. As MHLW is imposing this change on us, we will have a departure from the CDS in Japan, as we do in Europe, Italy, New Zealand, and US.

Please do not hesitate to ask us for additional information to support your case. As you know, it is imperative that we distinguish ourselves from the issues olanzapine faces.

Best Regards,

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-----Original Message-----
From: Izuishi, Koji
Sent: Wednesday, October 02, 2002 7:55 AM
To: Mitani, Michiyo; Melville, Margaret G; Brecher, Martin; Leong, Ronald

Cc: Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Bowen, Rebecca; Street, Paul R; Ose, Kazuyuki; Nakajo, Hirochika; Togashi, Motoya; Sawai, Etsuko

Subject: RE: Safety Division (MHLW) Instruction on Seroquel JPI concerning Diabetes Mellitus

Dear All

I strongly supports Mitani-san's letter ' we should Considering the tone of the instruction, we cannot avoid JPI revision.'.

If the agreement or submission of the draft amendments of JPI later than end of Oct, it will be triggered the worst scenario that MHLW strongly requires us as same indication as Olanzapine did.
Therefore defusing a crisis, we have to proactive JPI amendments and get the consultation or agreements with MHLW on schedule.

Regards
K.Izuishi (ex3819)
AstraZeneca K.K

-----Original Message-----
From: Mitani, Michiyo
Sent: Wednesday, October 02, 2002 7:17 PM
To: Melville, Margaret G; Brecher, Martin; Leong, Ronald
Cc: Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Bowen, Rebecca; Street, Paul R; Ose, Kazuyuki; Nakajo, Hirochika; Izuishi, Koji; Togashi, Motoya; Sawai, Etsuko
Subject: Safety Division (MHLW) Instruction on Seroquel JPI concerning Diabetes Mellitus

Dear All,

Thank you very much for the study 0041 information. We planned to wait for the GPT assessment until November, but, today, MHLW telephoned us and gave instruction to examine JPI revision, since reports of domestic diabetic cases are increasing.

Twelve Japanese cases have been reported to MHLW and HQ (Clintrace Nos of some cases are not available, so please refer our local nos for them):
Hyperglycaemia: 6 cases: serious - 200103951(2001AP04051), 200204425, 200205593, 200205220, 200205325(2002AP02947), moderate - 200203006
Diabetes mellitus: 1 case: serious - 200200382(2002AP00269)
Diabetic ketoacidosis: 4 cases: fatal - 200202573(2002AP01163), 200203342(2002AP01772)
serious - 200203901, 200203907(2002AP02304)
Possible diabetic ketoacidosis: 1 case: fatal - 200205214(2002AP02883)

MHLW instructed us to visit them, after reviewing all of the above cases comprehensively, in order to explain AZKK's action to be taken regarding JPI revision. We have to visit them by the end of October. Would you please give your comments on the above 12 cases and diabetic cases in other countries by 14 Oct.

Submission of the result of the study 0041 is not requested this time. However, it would be very much helpful if the GPT assessment of the study is available before we visit them.

Considering the tone of the instruction, we cannot avoid JPI revision. You sent us following mail of proposed amending of JPI. We believe that you

can accept our JPI revision if the revised wording is prepared based on your comments in this mail. So, we plan to negotiate with MHLW based on your comments. However, please understand that more strict wording could be imposed by them.

<< Message: Seroquel Hyperglycaemia — proposed responses to MHLW — Global Product Team comment to many issues! >>

P.S. As I told you before, MHLW asks us the reason why Seroquel CDS is not revised, though EU SmPC revision has been issued. Would you tell us if you have any plan the CDS is revised. If CDS is revised, we can revise JPI according to the revised CDS wording.

Thank you in advance for your assistance and we look forward to hearing from you.

Kind regards,
Michiyo

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

From:	Melville, Margaret G
Sent:	Wednesday, September 25, 2002 9:10 AM
To:	Ose, Kazuyuki; Nakajo, Hirochika; 'Sumie Ishiguro'; Mitani, Michiyo; Izuishi, Koji
Cc:	Brecher, Martin; Fitton, Lesley R; Oldham, Alex; Schwartz, Jack A; Leong, Ronald; Bowen, Rebecca; Street, Paul R
Subject:	Fasting Glucose Results of Seroquel Trial 0041

Dear All,

We would like to apologise that it has taken so long for us to respond to your request for fasting blood glucose data from Trial 0041. We have been analysing the results of the fasting glucose in Study 0041 and they are not clear. The results show that there was a 10 mg/dl increase in one of the 5 seroquel groups and that overall there was a minimal increase in blood glucose. These results are consistent with previous results of random blood glucose measurements, and it appears that samples were taken after the noon hour in an estimated 30% of patients. So the data do not add a lot to our current understanding of blood glucose, unfortunately!

I understand from your note Ose-san that you will need to send these results to MHLW. I think it is because we informed them that the reason that there was no information in the UK label on hyperglycaemia or diabetes mellitus is because we would be giving the UK Health Authority results from Study 0041 before a decision would be made on what would be in the UK label. I am sure that MHLW would also like to see these results to make sure what is in the JPI is good too.

However, the GPT has much work to do in understanding the results of Study 0041. The data are complex and it is taking more time to analyse. Is the Japanese team all right while we do more thinking on the data? We plan to have more information in November to give to you on these data.

Is it o.k.?

Best Regards,

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