

To: CN=Masashi Takahashi/OU=AP/O=LLY@Lilly
CC: CN=Masao Amano/OU=AP/O=LLY@Lilly; CN=Eric K Berger/OU=AM/O=LLY@Lilly; CN=Akito Kume/OU=AP/O=LLY@Lilly; CN=Mark Lakshmanan/OU=AP/O=LLY@Lilly; CN=Ronald K McPherson/OU=AP/O=LLY@Lilly; CN=Masashi Takahashi/OU=AP/O=LLY@Lilly; CN=Yoko X1 Tanaka/OU=AM/O=LLY@Lilly; CN=Lisa A Vierhile/OU=AM/O=LLY@Lilly
Date: 10/05/2000 02:20:44 PM
From: CN=Charles M Beasley Jr/OU=AM/O=LLY
Subject: Re: Priority AAA ! :Urgent ! Level-1-2 weight gain question
Attachments: EC question-level-1-2 revised Oct-05-00.doc; Reply to MHW_Glucose_Weight Gain 9-26-0.doc

You will have seen my previous messages regarding the draft response and changes in PI. I cannot approve the changes suggested in this draft of PI because weight gain and diabetes are placed in the same "basic precaution". However, if this is split into 2 basic precautions then I believe we are where we need to be. I suggest the following:

~~1. Cautious administration (olanzapine should be administered cautiously in the following patients)~~

~~(4) Patients with diabetes mellitus and those with risk factors of diabetes mellitus (family history of diabetes mellitus, obesity etc.)
[hyperglycemia or diabetes mellitus may worsen]~~

2. Important basic precautions

(1) As olanzapine may increase body weight, pay attention to obesity, and consider the diet therapy and exercise therapy if any sign of obesity is noted.

(2) Administer olanzapine with appropriate clinical care in patients with diabetes mellitus and those with risk factors for diabetes mellitus (family history of diabetes mellitus, obesity, etc).

4. Adverse reactions

(1) Important adverse reactions

3) ~~Hyperglycemia Diabetic coma, diabetic ketoacidosis:~~ The events of hyperglycemia could occur. ~~resulting in~~ Cases of diabetic coma or diabetic ketoacidosis have been reported.



Masashi Takahashi
10/05/2000 04:36 AM

To: Charles M Beasley Jr/AM/LLY@Lilly, Yoko X1 Tanaka/AM/LLY@Lilly, Eric K Berger/AM/LLY@Lilly
cc: Akito Kume/AP/LLY@Lilly, Masao Amano/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Ronald K McPherson/AP/LLY@Lilly
Subject: Priority AAA ! :Urgent ! Level-1-2 weight gain question

Dear Dr.Beasley, Yoko-san, Berger-san

We are not sure whether you have discussed this matter but I would like to send you our rivised version of this response based upon our "Precaution for Use"meeting today involving Drug Safety Unit, Regulatory, Dr.Kume, Medical Information Survice that is requested by our local SOP.

Our conclusion is

- 1) Kobe cannot make any decision on this matter locally therefore we will follow global Zyprexa team decision.
- 2) However, as Kume-sensei mentioned in his mail, we are sure that EC/MHW requests to rank weight gain (and hyperglycemia) issues higher in the safety section of package insert because MHW recognizes that olanzapine causes weight gain more than other antipsychosis and weight gain is a widely accepted risk factor for diabetes.
- 3) EC/MHW's request is based on SPC description which is included in submitted GAIYO. That is ;
 - 4.4. Hyperglycemia or exacerbation of pre-existing deabetes 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 in advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.
- 4) We want to avoid a request from MHW of forced blood glucose monitoring at launch. So, we think, it would be clever to make a deal with MHW by ranking weight gain (and hyperglycemia) at higher places so as to look similar to SPC description and also by stating our PMS plan clearly regarding the evaluation issues, the sample size and the study period.

The following is our revised proposal regarding pre-caution for use in Japanese P.I. The revised points are :

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1) We downgraded the text from #1 (Caution administration) to #2 (Important basic precautions) because we have only 2 cases in local studies.

2) The text of "hyperglycemia" should not be changed in the section of adverse reaction that had been approved before..

~~1. Cautious administration (olanzapine should be administered cautiously in the following patients)~~

~~(4) Patients with diabetes mellitus and those with risk factors of diabetes mellitus (family history of diabetes mellitus, obesity etc.) [hyperglycemia or diabetes mellitus may worsen]~~

2. Important basic precautions

(1) As olanzapine may increase body weight, pay attention to obesity, and consider the diet therapy and exercise therapy in patients with diabetes mellitus and those with risk factors of diabetes mellitus (family history of diabetes mellitus, obesity etc.) ~~if any sign of obesity is noted.~~

4. Adverse reactions

(1) Important adverse reactions

3) ~~Hyperglycemia Diabetic coma, diabetic ketoacidosis.~~ The events of hyperglycemia could occur. ~~resulting in~~ Cases of diabetic coma or diabetic ketoacidosis have been reported.

The attached is our revised response. Could you please let us know your comment or alternative answer or approval on this by tomorrow as Japan time.

As we mentioned previously, We have informed to EC that we will submit our responses on Oct. 11 because they strongly requested. That means, if we cannot provide the responses by Oct. 10, we cannot submit them to EC on Oct. 11, therefore, our olanzapine will NOT be reviewed at MHW Special committee on November 17th at which Sumitomo's Perospirone will be discussed. The approval of olanzapine will delay.

(We know that Zeneca's Quetiapine will be reviewed at MHW Special committee on October 23th.)

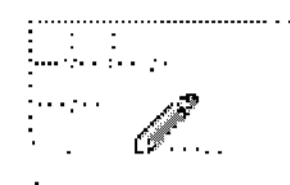


EC question-level-1-2 revised Oct-05-00.doc

Thank you for your help in advance.

Kind regards, --- Takahashi

----- □□□: Masashi Takahashi/AP/LLY □□□: 2000/10/05 17:23 -----



Masashi Takahashi
2000/10/05 00:57

□□: Charles M Beasley Jr/AM/LLY@Lilly
cc: Akito Kume/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Masao Amano/AP/LLY@Lilly, Ronald K McPherson/AP/LLY@Lilly
□□: Re:Urgent ! weight gain question

Dear Dr.Beasley,

I am not sure whether Dr.Kume had received your comments on this response doc. since I was in Tokyo today, but if not, please let us know your insight on this matter as soon as possible. Tomorrow afternoon, we will have the internal official meeting with DSU to discuss draft level of olanzapine considering EC's current position.

As we already informed EC that we plan to submit the responses on Oct.11, we think we should decide what is the best for us regarding this matter.

Thank you for your support always.

Kind regards, --- Takahashi

----- □□□: Masashi Takahashi/AP/LLY □□□: 2000/10/05 00:43 -----



Masashi Takahashi
2000/10/03 23:22

□□: Charles M Beasley Jr/AM/LLY@Lilly
cc: Akito Kume/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Masao Amano/AP/LLY@Lilly
□□: Urgent ! weight gain question

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Dear Dr.Beasley,
Dr.Kume would like to ask you to review our draft response Level-1-2(weight gain).
Since he has trouble at home, I am sending the Word file with his message to you instead.

Please read Dr.Kume's message at first and review and comments on this response as soon as possible.

<<deleted>>

Kind regards,
Takahashi for Dr.Kume

----- □□□: Masashi Takahashi/AP/LLY □□□: 2000/10/03 23:16 -----



Kazuyo Kume <kkume@quartz.ocn.ne.jp> 2000/10/03 23:05:35

□□: charles_beasley@lilly.com
cc: Masashi Takahashi/AP/LLY@Lilly, Masao Amano/AP/LLY@Lilly, Akito Kume/AP/LLY@Lilly
□□: weight gain question

Dr. Beasley

I ask a favor of you.

Could you review a draft of response document being sent tonight around 8pm
and, if you could, please send back your comment to us within tonight?

The draft is response to level 1-2 which is about hyperglycemia issue. I
made an English version of the draft at office, brought it back to home in
my laptop, and I found my laptop does not work well. So, I cannot send
draft at this moment, and I will do it at office first in the morning

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tomorrow. It should be around 8pm in Indy.

We Kobe team discussed for some length of time over the contents of draft including style, expression, and we reached at the following consensus.

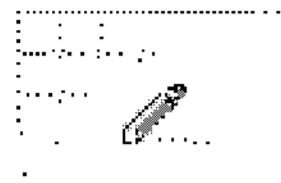
1. In theory, we agree on your conclusion that no special mention regarding weight gain and diabetes is warranted in the label at this time.
2. However, MHW requests to rank weight gain and hyperglycemia issues higher in the safety section of package insert because MHW recognizes that olanzapine causes weight gain more than other antipsychosis and weight gain is a widely accepted risk factor for diabetes.
3. MHW's request is based on SPC description which is included in submitted GAIYO.
4. We want to avoid a request from MHW of forced blood glucose monitoring at launch. So, team thinks, it would be clever to make a deal with MHW by ranking weight gain and hyperglycemia at higher places so as to look similar to SPC description and also by stating our PMS plan clearly regarding the evaluation issues, the sample size and the study period.

I apologize for not attaching draft here and I again ask a favor of you about a review today.

Sincerely

Akito

Please do not return to this address. This is my home email address



Akito Kume
2000/09/28 12:28

□□: Yoko X1 Tanaka/AM/LLY@Lilly
cc: Masao Amano/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Masakazu Takeuchi/AP/LLY@Lilly, Charles M Beasley Jr/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly
□□: Level I-2 Weight gain and Hyperglycemia

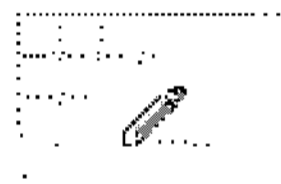
Yoko-san

Thank you for a nice, clear outline. This is helpful. I will send English version of response in 2-3 days.

regards

Akito

----- □□□: Akito Kume/AP/LLY □□□: 2000/09/28 12:23 -----



Yoko X1 Tanaka
2000/09/27 06:20

□□: Masao Amano/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Akito Kume/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Masakazu Takeuchi/AP/LLY@Lilly
cc: Charles M Beasley Jr/AM/LLY@Lilly, Yoko X1 Tanaka/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly
□□: Level I-2 Weight gain and Hyperglycemia

Hello,

We put together the draft outline based on some available references to answer this question.

We hope this will be of some help. If you have any questions, please let us know.



Reply to MHW_Glucose_Weight Gain 9-26-0.doc

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Regards,
Yoko

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