

To: CN=Masao Amano/OU=AP/O=LLY@Lilly
CC: CN=Charles M Beasley Jr/OU=AM/O=LLY@Lilly; CN=Jeffrey T Ramsey/OU=AM/O=LLY@Lilly;
CN=Yoko X1 Tanaka/OU=AM/O=LLY@Lilly; CN=Anna Thornton/OU=AM/O=LLY@Lilly; CN=Lisa
A Vierhile/OU=AM/O=LLY@Lilly
Date: 10/17/2000 05:03:08 PM
Subject: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Amano-san,

The FDA document is attached. Since it is a very large document, it has been divided into 4 files.

*** Final Report Sections 1-4, 5, 6-9.doc moved to H:\Mail\
*** Final Report Master Table.doc moved to H:\Mail\

Due to technical limitations, 3 tables are not contained in the electronic copy:

7.14

7.17

7.19

I can either send paper copies of these tables to you by DHL or I can send by fax. Please reply with your address or phone number so that I may send the missing tables to you.

Best regards,
Mark Millikan
Zyprexa Product Team



Masao Amano
10/17/2000 05:48 AM

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To: Charles M Beasley Jr/AM/LLY@Lilly, Mark D Millikan/AM/LLY@Lilly
cc: Masashi Takahashi/AP/LLY@Lilly, Lisa A Vierhile/AM/LLY@Lilly, Akito Kume/AP/LLY@Lilly, Mark Lakshmanan/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Mikihito Kosuge/AP/LLY@Lilly, Ichiro Obi/AP/LLY@Lilly, Yukari Ohno/AP/LLY@Lilly

Subject: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Beasley-san,

Thank you very much for your suggestion. Now I am preparing the response document based on CPMP document for the occasion that EC require us quicker response. I am also looking forward to obtaining the document "full FDA document dated May 1, 2000".

Millikan-san,

I am Masao Amano, Regulatory, Zyprexa Product Team, ELJ K.K. In Japan Zyprexa is now being reviewed for approval application by our government. Evaluation Center, an organization in Ministry of Health and Welfare, required us the data on hyperglycemia related to olanzapine administration. We would like to obtain the document "full FDA document dated May 1, 2000" by tomorrow morning, Japan time. Would you kindly send it to me electronically.

Best regards,

Masao



Charles M Beasley Jr
2000/10/17 02:19

□□: Masao Amano/AP/LLY@Lilly
cc: Akito Kume/AP/LLY@Lilly, Mark Lakshmanan/AP/LLY@Lilly, Mark D Millikan/AM/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Lisa A Vierhile/AM/LLY@Lilly
□□: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Mark is sending the US sections. With my initial response you should be able to select appropriate cases. However, you did not ask about several cases which were probably secondary cases of hyperglycemia. These can be determined by reading the introductory comments to the 3 sets of tables (deaths, coma without death, acidosis without death or coma). You will note that in the response that I sent today, additional cases were identified as secondary (under coma and hyperglycemia) we will review all coma and acidosis cases to find any additional potential secondary cases.

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Charles



Masao Amano
10/13/2000 08:58 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc: Masashi Takahashi/AP/LLY@Lilly

Subject: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Beasley-san,

Thank you very much for your kind cooperation.

Concerning previous e-mail dated Oct. 12th, I would like to ask again about Question 2 from EC.

The cases of diabetic coma are shown in Table 15/16 including suspected cases or cases not denied as cases of diabetic coma. There are no cases of diabetic coma in Table 17/18. To list the cases of diabetic coma, which cases would be added as cases of diabetic coma from Table 13/14?

Also the cases of diabetic ketoacidosis are shown in Table 17/18 including suspected cases or cases not denied as cases of diabetic ketoacidosis. To list the cases of diabetic ketoacidosis, which cases would be added as cases of diabetic ketoacidosis from Table 13/14 and 15/16?

Would you please tell us which cases should be selected as cases of diabetic coma and diabetic ketoacidosis.

*** Diabetic coma-ketoacidosis supporting documentation.pdf moved to H:/Mail/

Best regards,

Masao

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Masao Amano
2000/10/12 21:30

□□: Charles M Beasley Jr/AP/LLY@Lilly, Lisa A Vierhile/AP/LLY@Lilly
cc: Patrick McAndrews/AP/LLY@Lilly, Yasuko Hanahisa/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Akito Kume/AP/LLY@Lilly, Ronald K
McPherson/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Mikihito Kosuge/AP/LLY@Lilly, Ichiro Obi/AP/LLY@Lilly, Yukari Ohno/AP/LLY@Lilly
↓↓: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Beasley-san, Vierhile-san,

We have two questions from Dr. Matsuura of EC. These are as follows;

1. Provide the list of serious adverse events (cases) of hyperglycemia (including diabetes mellitus)
2. Show the cases which diabetic coma or diabetic ketoacidosis were observed

For Question 1, I think serious cases are those listed in Table 13/14 and Table 15/16 in "Supporting Documentation for the Addition of Diabetic Coma and Diabetic Ketoacidosis". Is my understanding correct?

For Question 2, in Table 13/14, Table 15/16 and Table 17/18, should I select only the cases which are described just "diabetic coma" and "diabetic ketoacidosis" or not?

In Table 14, GBS990904138 describes "coma". Does coma mean "diabetic coma"?

US000338270 describes "ketoacidosis". Does ketoacidosis mean "diabetic ketoacidosis"?

US97022578A describes "coma". Does coma mean "diabetic coma"?

US97121726A describes "coma". Does coma mean "diabetic coma"?

US98024165A describes "ketoacidosis". Does ketoacidosis mean "diabetic ketoacidosis"?

US990725729 describes "coma". Does coma mean "diabetic coma"?

US000337604 describes "suspected ketoacidosis". Does this mean "suspected diabetic ketoacidosis"?

In Table 16, US97021057A describes "diabetic acidosis". Is this regarded as "diabetic ketoacidosis"?

US97054048A describes "coma". Does coma mean "diabetic coma"?

US981012355 describes "coma". Does coma mean "diabetic coma"?

US990725071 describes "coma". Does coma mean "diabetic coma"?

US000134310 describes "coma". Does coma mean "diabetic coma"?

US980910808 describes "coma". Does coma mean "diabetic coma"?

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US990319151 describes "coma". Does coma mean "diabetic coma"?
DE981100634 is the case of "severe acidosis". This is not the case of "(severe) diabetic ketoacidosis", is it?
US990522804 describes "coma". Does coma mean "diabetic coma"?
US98015059A describes "sommolence or stupor". Is somnolence or stupor regarded as "diabetic coma"?
US980503939 describes "sommolence". Is somnolence regarded as "diabetic coma"?
DE991201851 describes "sommolence". Is somnolence regarded as "diabetic coma"?
US990624169 describes "syncope". Is syncope regarded as "diabetic coma"?
US990116671 describes "asthenia". Is asthenia regarded as "diabetic coma"?

In Table 18, EWC990603740, US000134444, US000336807, US000338253 describe "ketoacidosis". Does ketoacidosis mean "diabetic ketoacidosis"?
US000439362 describes "diabetic acidosis". Does diabetic acidosis mean "diabetic ketoacidosis"?
US000440162 describes "ketoacidosis". Does ketoacidosis mean "diabetic ketoacidosis"?
US97072944A describes "diabetic acidosis". Does diabetic acidosis mean "diabetic ketoacidosis"?
US97074243A describes "metabolic acidosis". Does metabolic acidosis mean "diabetic ketoacidosis"?
US97084135A describes "ketoacidosis". Does ketoacidosis mean "diabetic ketoacidosis"?
US990725129 describe nothing about diabetic ketoacidosis.

And please let us know the followings. These are questions from us?

In obesity in Table 14, what is the unit "stone" in GBS990904138?

In Peak Glucose Level at Time of Adverse Event in Table 18, what does 551"t" mean in US981011107?

In Peak Glucose Level at Time of Adverse Event in Table 18, what does 713"r" mean in US990725399?

We are required quick response to EC. We need your support.

Best regards,

Masao



Charles M Beasley Jr
2000/10/12 02:07

□□: Masashi Takahashi/AP/LLY@Lilly

cc: Lisa A Vierhile/AM/LLY@Lilly, Patrick McAndrews/AM/LLY@Lilly, Masao Amano/AP/LLY@Lilly, Yasuko Hanahisa/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Mark Lakshmanan/AP/LLY@Lilly, Akito Kume/AP/LLY@Lilly, Ronald K McPherson/AP/LLY@Lilly
□□: Re: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

I believe our supporting documentation covers it best. The latest review is covered in the comprehensive review submitted to FDA (you have copy I believe). If I recall correctly there were: 15 deaths; 22 non-fatal comas; 53 non-fatal, non-coma acidosis cases. In several of these the hyperglycemia was clearly secondary to a process other than olanzapine influence on insulin secretion or insulin receptor function. For example, these numbers include cases of pancreatitis, etc.
Charles



Masashi Takahashi
10/11/2000 09:47 AM

To: Charles M Beasley Jr/AP/LLY@Lilly, Lisa A Vierhile/AM/LLY@Lilly, Patrick McAndrews/AM/LLY@Lilly
cc: Masao Amano/AP/LLY@Lilly, Yasuko Hanahisa/AP/LLY@Lilly, Masashi Takahashi/AP/LLY@Lilly, Mark Lakshmanan/AP/LLY@Lilly, Akito Kume/AP/LLY@Lilly, Ronald K McPherson/AP/LLY@Lilly

Subject: EC questioned Hyperglycemia, Diabetic Coma and Diabetic Ketoacidosis

Dear Dr. Beasley and Vierhile-san,

Evaluation Center called Kobe office at 5:30 pm after review of our response Level-1-2 and precaution for use in our draft P.I. that we had just submitted. They wanted to know ASAP whether or not there were severe cases of diabetic coma and diabetic ketoacidosis.

Since Amano-san was in Shinkansen and I am in Tokyo, we talked by mobile phone and agreed upon to ask Hanahisa-san (regulatory) to fax the following documents/information. She faxed them to EC on 8:30 pm.

- 1) Supporting documentation for the addition of diabetic coma and diabetic ketoacidosis (affiliate olanzapine CDS distribution June 2000) 27 pages
- 2) ADR reports (diabetic ketoacidosis) that we had submitted to EC (No.200000065,200002826,AEOLA0001059)
- 3) Lee E Goldstein, M.D., et. al., New-Onset Diabetes Mellitus and Diabetic Ketoacidosis Associated With Olanzapine Treatment, Psychosomatics 40:5 438-443, 1999 (We've submitted this paper with the response level-1-2)

Since we want to avoid any request from MHW of forced blood glucose monitoring at launch, please help us if EC has more question/concern in terms of this matter.

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Thank you for your continuous support.

kind regards,

Takahashi/Hanahisa/Amano

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