

To: CN=Noriko Akagi/OU=AP/O=LLY@Lilly
CC: CN=Neil W Aubuchon/OU=AP/O=LLY@Lilly; CN=Russell L Barton/OU=AM/O=LLY@Lilly;
CN=Anne Bille/OU=AP/O=LLY@Lilly; CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=James L
Gahimer/OU=AM/O=LLY@Lilly; CN=Kei Kikuchi/OU=AP/O=LLY@Lilly; CN=Akira
Kokan/OU=AP/O=LLY@Lilly; CN=Ludmila Kryzhanovskaya/OU=AM/O=LLY@Lilly; CN=Jeffrey T
Ramsey/OU=AM/O=LLY@Lilly; CN=Koichi Saida/OU=AP/O=LLY@Lilly; CN=Hiromasa
Tara/OU=AP/O=LLY@Lilly; CN=Arne Van Teunenbroek/OU=AP/O=LLY@Lilly; CN=Andrew J
Wood/OU=AP/O=LLY@Lilly
BCC: CN=Jared G Kerr/OU=AM/O=LLY
Date: 10/24/2002 12:29:07 PM
From: CN=Jared G Kerr/OU=AM/O=LLY
Subject: Re: ?Comments from MHLW?Cases with hepatic disorder

Akagi-san:

This is great news! While the additional comments from the MHLW officer are not surprising it is good insight into their thoughts. Nonetheless, it does not diminish the true success of ELJKK and Global working together through the Safety Response process. Thanks to everyone working as a team with a set goal we were able to quickly and effectively provide to MHLW answers that matter on their questions of hepatic AEs. The truly excellent clinical expertise that was provided from both parts of the globe was invaluable.

Please accept a round of applause from our team to you and your colleagues.

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Page: 1 of 15

Noriko Akagi

10/23/2002 12:53 AM

To: Patrizia Cavazzoni/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly
cc: Anne Bille/AP/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Koichi Saida/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Arne Van Teunenbroek/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
Subject: ☐Comments from MHLW☐Cases with hepatic disorder

Dear all,

The officer of the MHLW called me today and said that NO labeling change was necessary at present (below e-mail).

In addition to the comments I wrote in my e-mail below, she mentioned our causality assessment. She said that some cases assessed as 'unrelated' or 'unlikely' by us did not seem to be so, even though there had been some confounding factors in the cases.

As we exchange e-mails on this matter on October 1, there seems to be a gap derived from cultural differences between the US and Japan. From the view point of MHLW, a typical Japanese way of thinking, Lilly seem to choose the way of too much strong denial of causality between the drug and AE, and attributing AEs to the other factors. Under the situation, MHLW may conclude that Lilly always hesitate to take safety actions.

Objective of this e-mai is to let you know the cultural differences for your information.

with regards,
Noriko Akagi

----- ☐☐☐: Noriko Akagi/AP/LLY ☐☐☐: 02/10/23 13:38 -----

Noriko Akagi

02/10/23 13:39

☐☐☐: Neil W Aubuchon/AP/LLY@Lilly, Anne Bille/AP/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Markus R Saba/AP/LLY@Lilly, Koichi Saida/AP/LLY@Lilly, Katsunori Tanaka/AP/LLY@Lilly, Takashi Taniguchi/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Arne Van Teunenbroek/AP/LLY@Lilly, Norihiko Tonooka/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
cc: ☐☐☐: ☐Comments from MHLW☐Cases with hepatic disorder

Page: 2 of 15

Wood/AP/LLY@Lilly, Yasuko Kojima/AP/LLY@Lilly, Keiichi Enomoto/AP/LLY@Lilly, Tsuneaki Saito/AP/LLY@Lilly, Yumi Kinoshita/AP/LLY@Lilly, Mayumi Yamada/AP/LLY@Lilly, Akemi Mera/AP/LLY@Lilly, Masaaki Doi/AP/LLY@Lilly

□□: □Intrime repor□Cases with hepatic disorder-NO response has been received.

Dear all,

The report about cases with hepatic disorder of ZYP was submitted on Oct. 2. On Oct 4, the officer sent me e-mail telling me to wait for a while.

It has been a week since the submission, but the MHLW has NOT contacted me except the e-mail of Oct.4.

We will let you know any comments from the MHLW when it comes.

with regards,
Noriko Akagi

----- □□□: Noriko Akagi/AP/LLY □□□: 02/10/09 17:42 -----

Noriko Akagi

02/10/02 23:31

cc: □□: Jared G Kerr/AM/LLY@Lilly
Akira Kokan/AP/LLY@Lilly, Anne Bille/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly

□□: Re: review for 15 cases with serious hepatic disorder

Kerr-san

Thanks for all of your cooperation, we sent the MHLW our comments on the Japanese cases and an overall conclusions by fax today. The overall conclusion lined with Indy's written in your e-mail of Sept 26.

Since the report sent late at night, I have not received any response from the MHLW. When we receive any comments from the MHLW, I will let you know ASAP.

Page: 4 of 15

Again, I appreciate you, Jim, Ludmila and all the people involved in this matter.

with regards,
Noriko Akagi

Jared G Kerr

02/10/02 04:12

cc: □□: Noriko Akagi/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly
Anne Bille/AP/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei
Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiromasa
Tara/AP/LLY@Lilly
□□: Re: review for 15 cases with serious hepatic disorder

Ueno-sensei and Akagi-san:

We understand and appreciate your situation. May we offer this fair and final compromise that should adequately meet your needs while appropriately defining the causality. "Can not be excluded" is technically correct but not as good as an explanation as "unlikely".

Therefore, for the patient in question (200206571) may we suggest the following: "Cannot be excluded but causality unlikely".

However, if you find this is still not appropriate we agree to the use of your text: "Cannot be excluded".

I hope you will find this compromise acceptable. Please keep us updated as to the progress of this issue.

Thank you for your hard work and diligence.

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Hiroshi Ueno

10/01/2002 05:34 AM

To: Jared G Kerr/AM/LLY@Lilly
cc: Akira Kokan/AP/LLY@Lilly, Anne Bille/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Noriko Akagi/AP/LLY@Lilly
Subject: Re: review for 15 cases with serious hepatic disorder

Kerr-san

Thank you very much for your help.

As for the case (200206571), we still think it is difficult to explain the causality assessment as 'unlikely'. We have almost agree your answer. But some points are different.

(1) The most likely offending agents were the neuroleptics. (Indy)

We think Olanzapine and other 2 neuroleptics are equally suspected for liver dysfunction.

(2) Olanzapine is only one of 6 drugs in this case known to have an effect on liver functions (Indy).

I completely agree with it.

But this reason does not explain the causality of "unlikely". In Japanese way of thinking, the number of suspected drugs does not diminish the causality of Olanzapine.

So in this case causality assessments remains 'cannot be excluded', I think.

Could you understand and accept this different cultural background?

If you could accept our opinion, we would like to assess this case as "cannot be excluded".

We are looking forward to hearing from you ASAP, hopefully, Oct 1 (Indy time).

Your cooperation is always appreciated.

Regards.

Page: 6 of 15

Hiroshi Ueno, M.D.

safety physician
Medical and Drug information
Lilly Research Laboratories Japan
Eli Lilly Japan K.K.

Noriko Akagi

02/10/01 18:31

cc: □□: Jared G Kerr/AM/LLY@Lilly
Anne Bille/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly

Re: review for 15 cases with serious hepatic disorder

Kerr-san

Thank you for your coordination.

Jim and Ludmila

Thank you again for your cooperation.

We, however, still think it is difficult to explain the causality assessment as 'unlikely' on the case (200206571), because olanzapine seems to be one of the drugs which was attributable to the event.

Ueno-san will explain PV's assessment and standpoint.

Your cooperation is always appreciated.

with regards

Page: 7 of 15

Noriko Akagi

Jared G Kerr

02/09/28 06:08

cc: □□: Noriko Akagi/AP/LLY@Lilly
Anne Bille/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly

Re: review for 15 cases with serious hepatic disorder

Akagi-san:

Please find attached file with answers from Jim Gahimer and Ludmilla.

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Noriko Akagi

09/27/2002 05:32 AM

To: James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly
cc: Anne Bille/AP/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James A Edwards/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
Subject: Re: review for 15 cases with serious hepatic disorder

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Hi, Jim and Ludmila

Thank you very much for your quick response. Your comments are very helpful to understand the cases.

I still have one question.

As for Case 13(200206571), would you please write your comments why ZYP is 'unlikely' in the cell of 'Answer from Indy'. I understand the neuroleptics is more likely related to the AE. But I think ZYP is also attributable to the AE.

Thank you very much for your contribution on this matter in advance.

with regards,
Noriko Akagi

Jared G Kerr

02/09/27 08:24

cc: □□: Noriko Akagi/AP/LLY@Lilly
Anne Bille/AP/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James A Edwards/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly

□□: Re: review for 15 cases with serious hepatic disorder

Akagi-san:

Please find updated Excel spreadsheet with aligned comments from Jim Gahimer and Ludmilla Kryzhanovskaya.

They have provided the following:

- 1) 'Indy's causality assessment'
- 2) 'Answer to Kobe's questions'

Page: 9 of 15

Any specific questions on cases should be forwarded directly to Jim and Ludmilla. As you prepare your response please feel free to reformulate the responses so that they are more formal. I hope we were of useful assistance during this process. Thank you for your patience and cooperation. I think with the help of the Safety Response Process we have efficiently and effectively handled this issue. Please let me know if further refinements are necessary. Of course, as with any response please provide us a final version and update us on the issue as it progresses.

Best of luck!

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Noriko Akagi

09/26/2002 01:36 PM

To: James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly
cc: Anne Bille/AP/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James A Edwards/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
Subject: Re: review for 15 cases with serious hepatic disorder

Kerr-san
Thank you very much for your coordination. Your efforts are always appreciated.

Jim and Ludmila,

Page: 10 of 15

Thank you very much that both of you evaluated the 15 Japanese cases quickly. Sorry for not responding sooner because I did not have enough time to read the e-mail from Jared due to the visit to Dr. Fujii on Sept 26.

On the way back to Kobe, Ueno-sensei and I evaluated the 15 cases (before reading Jared's e-mail). After reading your assessment, there are not many differences between yours and us. However, there are some parts I would like to ask.

Therefore, I reformatted the table you made so that you would write your answer.

1) Please fill out the column of 'Indy's causality assessment'

2) Please fill out the column of 'Answer to Kobe's questions', which is next to the column of 'Questions from Kobe'. (Please keep in mind that these questions are just my questions, because I did not have time to discuss your assessment with Ueno-sensei. So, some questions are not scientific, sorry)

As for the case(200105102), I wrote the discontinuation date of the concomitant drugs (in red) for your information.

I would be grateful if you could send me your answer on Sept 26 (Indy time). Please accept my apology about such a short period.

Thank you very much in advance.

with regards,
Noriko Akagi

Jared G Kerr

02/09/26 07:55

cc: □□: Noriko Akagi/AP/LLY@Lilly
Anne Bille/AP/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James A Edwards/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
□□: Re: review for 15 cases with serious hepatic disorder

Akagi-san:

Page: 11 of 15

Please find attached the review of the identified cases of serious hepatic disorder in Japan by Jim Gahimer and Ludmilla Kryzhanovskaya. Please note that we have reformatted the document for our purposes. In addition, an overall conclusion has been written that states that any the following:

In Precautions (section 1) of the Japanese local label, careful administration is recommended in patients with liver disorders or patients who are being treated concomitantly with hepatotoxic drugs (can worsen liver disorder). In section 4 (Adverse reactions) of the Japanese local label, the laboratory test values of ALT elevation and AST elevation are listed as being observed in 15.8% and 11.5% of cases respectively. The estimated incidence of these events (including under reporting estimates) occurring spontaneously are far lower. In addition, the 15 cases reviewed do not contain any deaths or serious sequelae related to the hepatic events reported. In fact many of the events were resolving or resolved at the time of the report. It is also important to note that all 15 hepatic adverse event cases reviewed were confounded by concurrent medical conditions, concomitant medications, lack of information and negative dechallenges and rechallenges. In light of the above review of the 15 individual Japanese hepatic adverse event cases provided by the Japanese affiliate as well as the estimated incidence of hepatic events globally, it is felt that the present Japanese local label adequately reflects the known safety information regarding hepatic adverse events in association with olanzapine.

I hope you will find our assessment useful. Please keep us apprised of any further developments on this issue. Any specific questions on the Indy case review by the affiliate physicians should be directed to Jim and Ludmilla.

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Jared G Kerr

09/24/2002 04:37 PM

To: Noriko Akagi/AP/LLY@Lilly
cc: Anne Bille/AP/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, James A Edwards/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Jared G Kerr/AM/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly,

Page: 12 of 15

Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly

Subject: Re: review for 15 cases with serious hepatic disorder

Akagi-san:

Thank you for the forwarding this information to us. I think the Safety Response Process is working well. Thank you for using what we agreed upon. We have asked Jim Gahimer and Ludmilla Kryzhanovskaya to review the cases and provide comments. We are currently on Step 5 of the Safety Response Process (attached):

At this time, we are not aware that any Global data is needed. Ludmilla and Jim will formulate their responses and provide a single Lilly assessment of these cases through me (or proxy) by the deadline that you have requested (September 26, Japan time [Sept. 25 PM, Indy]). If we have any further questions I will let you know. Any physician to physician discussion should occur directly between the CRPs for global and Japan.

Sincerely,

Jared Kerr
Critical Issues-Customer Response Team
Zyprexa Product Team

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Noriko Akagi

09/24/2002 05:48 AM

To: Jared G Kerr/AM/LLY@Lilly
cc: Patrizia Cavazzoni/AM/LLY@Lilly, James L Gahimer/AM/LLY@Lilly, Ludmila Kryzhanovskaya/AM/LLY@Lilly, Hiroshi Ueno/AP/LLY@Lilly, Hiromasa Tara/AP/LLY@Lilly, Kei Kikuchi/AP/LLY@Lilly, Akira Kokan/AP/LLY@Lilly, Andrew J Wood/AP/LLY@Lilly
Subject: review for 15 cases with serious hepatic disorder

Kerr-san

Page: 13 of 15

As I mentioned in the previous e-mail, the MHLW asked about the serious hepatic disorder of ZYP.

Therefore, we have the following requests:

1) Indy's comments on each of the 15 Japanese cases. Please write Indy's comment in the right column in the attached table.

2) The number of cases with serious hepatic disorder worldwide.

There is no specified format. Just 'number of the cases', 'estimated number of exposed patients' and 'data cut-of-date' would be fine at present.

3) If Indy has comments on relation between ZYP and serious hepatic disorder, please let us know.

There is no specified format.

As for deadline, we would like to have your comments and the data mentioned above by Sept 26 (Japan Time). As you may know, the quicker response is better for the relationship with the MHLW.

You and I made a manual for this kind of situation. As for the above mentioned request #2 and #3, please follow the manual.

If you have any questions, please let me know.

with regards,
Noriko Akagi

[attachment "serious hepatic disorder .xls" has been removed by Jared G Kerr/AM/LLY]

[attachment "Japan Safety Response Proposal 12 March 2002.doc" has been removed by Jared G Kerr/AM/LLY]

[attachment "Japan Case Review 25 Sept 2002b.xls" has been removed by Noriko Akagi/AP/LLY]

[attachment "Questions to Indy on cases with hepatic disorder.xls" has been removed by Jared G Kerr/AM/LLY]

[attachment "Japan Case Review 26 Sept 2002.xls" has been removed by Jared G Kerr/AM/LLY]