Re: Actos [SEC=UNCLASSIFIED]
Nick Simpson to: [redacted] 17/06/2011 11:24 AM
Cc: Bronwen Harvey

Dear [redacted]

I forgot to ask in the teleconference: have you submitted to TGA the follow-up to PROactive, mentioned in Takeda's response to the KPNC cohort study?

Takeda has recently completed and submitted (under separate cover) the results from the 4-year
interim analysis of study AD-4833/EC-445, which is an ongoing, European, multicentre, observational study of subjects who were previously treated in PROactive (AD-4833/EC-444) with pioglitazone or placebo in addition to their existing antidiabetes and cardiovascular medication.

Since this apparently has a bearing on the issue of bladder cancer, would you be able to submit that data too (or if it has been submitted, would you mind providing a reference submission number)?

kind regards

Nick

.....
Nick Simpson MBBS MPH PhD

Medical Officer | Signal Investigation | Office of Product Review | Monitoring and Compliance Group
Therapeutic Goods Administration | Commonwealth Department of Health and Ageing

phone 02 6232 8092 | fax 02 6232 8392 | nick.simpson[redacted] | http://www.tga.gov.au

[redacted] Dear Nick Please find attached the translation... 17/06/2011 10:50:04 AM

From: [redacted]
To:
Cc: Bronwen.Harvey[redacted] Jane.Cook[redacted] Neil.Mitchell[redacted]
Nick.Simpson[redacted]
Date: 17/06/2011 10:50 AM
Subject: Re: Actos [SEC=UNCLASSIFIED]

Dear Nick

Please find attached the translation of the Afssaps analysis. I will send separately the meta-analysis discussed in our meeting this morning.

(See attached file: 917486_pioglitazone_final CNAMTs report translation with tables.doc)

Kind Regards

[redacted]

(Embedded image moved to file: pic18990.jpg)

[redacted]

15/06/2011 02:13 PM

To: Nick.Simpson[redacted]

cc: Bronwen.Harvey[redacted]
Jane.Cook[redacted]
Neil.Mitchell[redacted]

Subject: Re: Actos [SEC=UNCLASSIFIED] (Document link: [redacted])

Dear Nick

Thank you for the invitation to discuss this matter on Friday, I have provided a dial in number and passcode below which can be used from multiple locations if required. I have also attached an electronic copy of the KPNC interim analysis that was submitted in February.

A translated copy of the Afssaps report has been requested from Takeda, I hope to be able to provide it this week although Takeda have not confirmed this as yet. With regard to point 3 in your message below, can you clarify which cohort study you are referring to?

I look forward to speaking with you on Friday.

Conference Dial In #: [redacted]
Passcode: [redacted]

[attachment "kpnc-3rd-cohort-executive-summary[1].pdf" deleted by [redacted] [attachment "01-3-tl-opi-524-5-year-combined-report[1].pdf" deleted by Kim [redacted]

Kind Regards
[redacted]
(Embedded image moved to file: pic10002.jpg)

Nick.Simpson[redacted]
[redacted]

14/06/2011 02:29 PM

To: [redacted]

cc: Bronwen.Harvey[redacted]
Jane.Cook[redacted]
Neil.Mitchell[redacted]

Subject: Actos [SEC=UNCLASSIFIED]

Dear [redacted]

Thank you for sending information about BfArM's proposed course of action, while awaiting the EMA CHMP review.

The TGA plans to conduct a risk-benefit analysis for pioglitazone, taking into account the issue of bladder cancer.

More immediately, it appears necessary to update the PI / CMI concerning this potential risk:

- At the moment, there is a reference (in the Carcinogenicity, Mutagenicity and Impairment of Fertility section) to urinary bladder transitional cell tumours in rats, including the following statement: "Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans". The view that pioglitazone is "unlikely to pose a carcinogenic risk in humans" is out-of-date and this aspect of the PI should be modified.

- It also seems appropriate to include a new and separate Precaution regarding the risk of bladder cancer with pioglitazone use, based on information in (a) pre-clinical studies, (b) controlled trials (as discussed in the US Product Information), (c) the Kaiser Permanente Northern California cohort study and (d) the new French cohort study. Please note, the new French cohort study has not been reviewed by TGA, but preliminary information suggests that its results at least confirm those of the KPNC cohort study and are statistically significant. The TGA will consider the need for a Black Box warning regarding this safety issue.

Will representatives from Lilly be able to participate in a teleconference this Friday 17th June at 10am to discuss this issue? If so, please provide a telephone number and we will call you at approx 10am.
You may wish to consider what text should be included in the new Precaution titled "Risk of bladder cancer", e.g. an outline of data sources, the estimated relative and absolute risk, the need for appropriate clinical monitoring...

Also,
1. Would you be able to send an electronic copy of the document you sent to Dr Mitchell in February 2011 reporting findings of the Kaiser Permanente Northern California cohort study, where a dose and time dependent trend for bladder cancer was also seen?

2. Would you be able to send a certified translation into English of AFSSAPS's analysis (attached)?

3. Are you able to send an English version of the study report for the new cohort study?

Please call me on 02 6232 8092 if you want to discuss any of those issues.

kind regards

Nick

.....

Nick Simpson MBBS MPH PhD

Medical Officer | Signal Investigation | Office of Product Review | Monitoring and Compliance Group
Therapeutic Goods Administration | Commonwealth Department of Health and Ageing

phone 02 6232 8092 | fax 02 6232 8392 | nick.simpson[redacted]

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----- Forwarded by Nick Simpson/TGA/Health on 14/06/2011 12:38 PM -----

From: Neil Mitchell/TGA/Health
To: Nick Simpson/TGA/Health@TTRA
Date: 14/06/2011 12:05 PM
Subject: Fw: Actos [SEC=UNCLASSIFIED]

----- Forwarded by Neil Mitchell/TGA/Health on 14/06/2011 12:05 PM -----

From: [redacted]
To: Jane.Cook[redacted]
Cc: Neil.Mitchell[redacted]
Date: 14/06/2011 11:19 AM
Subject: Fw: Actos

Dear Dr Cook

As a result of the Afssaps decision to suspend pioglitazone-containing medicines, Germany's Federal Institute for Drugs and Medical Devices (BfArM) have issued advice that they intend to take the same course of action as the French authority.

Currently Eli Lilly are awaiting the outcome of discussion between Takeda and the agencies involved and will provide further updates as they are received from Takeda.

Kind Regards
[redacted]
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----- Forwarded by [redacted] on 14/06/2011 10:29 AM -----

[redacted]

10/06/2011 01:21 PM

To: Jane.Cook[redacted]
cc: Neil.Mitchell[redacted]
Subject: Actos

Dear Dr Cook

As you would most likely already be aware, the French Medicines Agency (Afssaps) has decided to suspend the use of pioglitazone-containing medicines in France. Currently Lilly Australia do not have any information other than that available via the EMA and Afssaps websites.

Lilly global are scheduled to meet with representatives from Takeda next week to request further information. As soon as any new information is available to Lilly, we will provide you with an update.

In the meantime, please do not hesitate to contact me if you have any questions.

Kind Regards

[redacted]

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[attachment "pic07172.jpg" deleted by [redacted] [attachment "pic02529.jpg" deleted by [redacted] [attachment "pioglitazone, Caisse National d'Assurance Maladie study report.pdf" deleted by [redacted]

[attachment "917486_pioglitazone_final CNAMTs report translation with tables.doc" deleted by Nick Simpson/TGA/Health] [attachment "pic18990.jpg" deleted by Nick Simpson/TGA/Health] [attachment "pic10002.jpg" deleted by Nick Simpson/TGA/Health]