R12/1074159

Actos PI and Dear HP Letter
[redacted] to: Bronwen.Harvey 27/06/2011 02:57 PM

History: This message has been forwarded.

4 attachments

DHCPL_for_Australia_v2.1_27Jun11.docx pic01842.jpg pic00288.jpg pic30106.gif

Dear Bronwen

Please find attached our final version of the Dear HP letter with the overseas regulatory section completed for actions relating to the US and EU.

(See attached file: DHCPL_for_Australia_v2.1_27Jun11.docx)

I have also just learned this morning that the Japanese Health Authority have announced changed to the PI for pioglitazone containing products (see blue text below). We did not include this in the Dear HP letter to avoid it becoming over complicated and lengthy.

We now await your decision on when the PI update can be implemented, once approved/acknowledged we can then proceed with mail out of the letter.

Important Precautions

In epidemiological studies conducted overseas in patients with diabetes mellitus, potential increased risk of bladder cancer was observed in patients who received pioglitazone. The risk tended to increase with long-term use. Therefore, caution should be exercised for the following points (See Other Precautions).

- ACTOS® Tablets should not be administered to patients with active bladder cancer. ACTOS® Tablets should be administered carefully to patients with a prior history of bladder cancer, by fully taking into account the benefit and risk of pioglitazone.
- Before initiating treatment, the patient or his/her family should be given a full explanation of the risk of bladder cancer. The patient must be instructed to immediately consult a physician when any sign or symptom of blood in the urine, urinary urgency, pain on urination, etc. is observed.
- Periodic examination, such as urinalysis, should be performed during taking ACTOS® Tablets. Appropriate measures should be taken when abnormality is observed. Also, careful observation should be continued after stop taking ACTOS® Tablets.

Other Precautions

In an interim analysis of an epidemiological study conducted overseas in patients with diabetes mellitus, full analysis did not show a significant difference in the risk of bladder cancer (hazard ratio 1.2 [95%CI 0.9 - 1.5]), however stratified analysis indicated a significant increase in the risk of bladder cancer for patients who received pioglitazone for 2 years or longer (hazard ratio 1.4 [95%CI 1.03 - 2.0]). Also, in another epidemiological study, the risk of bladder cancer was significantly increased in patients who were taking pioglitazone (hazard ratio 1.22 [95%CI 1.05 - 1.43]). In addition, there was a significantly increased risk of bladder cancer in patients who received pioglitazone for 1 year or longer (hazard ratio 1.34 [95%CI 1.02 - 1.75]).

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Kind Regards
[redacted]

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[redacted]
Medical Division
Eli Lilly Australia Pty Limited
112 Wharf Road West Ryde NSW 2114 AUSTRALIA
Ph: [redacted]
Fax:
W : www.lilly.com.au (Embedded image moved to file: pic00288.jpg)
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In the interests of PATIENT SAFETY if your email relates to an adverse event or a clinical trial adverse event, please contact the Product Safety department as soon as possible at AU_Drug_Safety[redacted] or phone +61 (0) 2 9325 4676.

XX June 2011

IMPORTANT SAFETY INFORMATION ON ACTOS® (pioglitazone hydrochloride)

Dear Healthcare Professional,

In agreement with the Therapeutic Goods Administration (TGA), Eli Lilly and Company would like to inform you of important new safety information regarding the use of ACTOS® (pioglitazone hydrochloride) and the potential risk of bladder cancer:

Summary

The PROactive study was a large, placebo controlled cardiovascular outcomes study that involved over 5200 patients. An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) of bladder cancer reported compared to 5 cases (0.2%) in the placebo arm; the point estimate for the hazard ratio (HR) was 2.7 (95% confidence interval [CI] 0.99-7.6). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

A recent five-year interim analysis of a cohort of 193,099 diabetic patients ≥40 yrs of age drawn from the Kaiser Permanente Northern California (KPNC) health plan found that, after adjusting for age, sex, use of tobacco products, use of other diabetic medications, and other risk factors, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to other patients was 1.2 (95% CI 0.9-1.5). The incidence of bladder cancer increased with increasing cumulative dose and duration of pioglitazone use. The hazard ratio for bladder cancer in subjects with 12-24 months of pioglitazone use (compared to subjects never exposed to pioglitazone) was 1.4 (95% CI 0.9-2.1). The hazard ratio after 24 months of pioglitazone use was 1.4 (95% CI 1.03-2.0). Based on these data, treatment with pioglitazone for longer than 12 months may be associated with 27.5 excess cases of bladder cancer per 100,000 person-years follow-up, compared to never use of pioglitazone and this risk may increase with further duration of therapy. The conclusions from these studies have not been tested in a purposefully designed prospective study.

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with pioglitazone.

Updates to Australian ACTOS® (pioglitazone hydrochloride) product information

The following information has been added to the Australian ACTOS® (pioglitazone) product information:

Precautions section

Bladder Cancer

An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there 5 cases (0.2%); the point estimate for the hazard ratio (HR) was 2.7

(95% confidence interval [CI] 0.99-7.6). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

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Based on epidemiological data, treatment with pioglitazone for longer than 12 months may be associated with 27.5 excess cases of bladder cancer per 100 000 person-years follow up, compared to never use of pioglitazone and this risk may increase with further duration of therapy. These conclusions have not been tested in a purposefully designed prospective study.

Pioglitazone should not be used in patients with bladder cancer or a history of bladder cancer. The risk of bladder cancer should be considered in the care of all patients treated with pioglitazone.

Adverse reactions identified from Clinical Trials section

Bladder Cancer

An increased incidence of bladder cancer was observed in subjects receiving pioglitazone in the PROactive study. In the pioglitazone arm there were 14 cases (0.5%) and in the placebo arm there were 5 cases (0.2%); the point estimate for the HR was 2.7 (95% CI 0.99-7.6). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm (see PRECAUTIONS, Bladder Cancer).

The following information (shown as strikethrough text) has been deleted from the product information as it is no longer accurate based on the new data.

Carcinogenicity, Mutagenicity and Impairment of Fertility

A two-year carcinogenicity study in mice showed no drug-related increases in tumour incidences at oral doses up to 91 mg/kg/day. Rats dosed orally with pioglitazone at 0.9-57 mg/kg/day for two years showed increased incidences of subcutaneous benign adipose tissue tumours (lipomas) and urinary bladder transitional cell tumours. Systemic exposure (plasma AUC_{0-24h}) to total active compounds at the highest dose in both studies was 8 times greater than that in humans at the maximum recommended dose. The no-effect doses were not established for either tumour site. Subcutaneous benign adipose tissue tumours (lipomas) have been observed in rats treated with other thiazolidinedione drugs, and are probably related to the pharmacodynamic activity of this drug class. ~~Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans.~~

To better understand any potential relationship between the use of ACTOS® (pioglitazone hydrochloride) and reports of adverse events, Eli Lilly will continue to carefully monitor adverse events through ongoing surveillance and analysis, in addition to ongoing epidemiologic investigations.

The regulatory actions being undertaken by international regulatory agencies

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are also reviewing information relating to pioglitazone and bladder cancer. The FDA has issued a statement indicating that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer, and caution prescribers against use of pioglitazone containing products in patients with active bladder cancer or a history of bladder cancer.

The EMA is currently reviewing data from multiple sources to assess the association between pioglitazone and bladder cancer risk. The Committe for Medicinal Products for Human Use (CHMP) have noted that three interim reports from the KPNC study have not confirmed a clear association between the use of pioglitazone and the occurrence of bladder cancer but that there is a signal of a potential increased incidence in those with longest exposure and highest cumulative dose. CHMP have reviewed additional epidemiological data and have concluded that there are still additional factors that need to be considered before it can form an opinion. Additional scientific advice will be sought with the CHMP's opinion expected in July 2011. Regulators in France and Germany have suspended use of pioglitazone containing medicines pending the outcome of the EMA review.

Call for Reporting

Healthcare professionals are reminded of the need to report any adverse reactions suspected to be associated with the use of ACTOS® (pioglitazone hydrochloride) to Eli Lilly Australia Global Product Safety by phone (02) 9325 4676, or facsimile (02) 9325 4320.

In addition, adverse events may be reported to the TGA via fax at 02 6232 8392, e-mail at adr.reports[redacted], by post to TGA, P.O. Box 100, Woden, ACT, 2606, by telephone (freecall within Australia) at 1800 044 114 or reported online at www.tga.gov.au .

Communication Information

Please contact your Eli Lilly Representative or the Medical Information Department on 02 9325 4622 if you have questions or if you wish to receive further information. A copy of the updated Product Information document can be obtained by contacting Eli Lilly or downloaded from the TGA website (www.ebs.tga.gov.au).

Yours Faithfully,
George Labib MD
Medical Advisor, Diabetes Business Unit
Eli Lilly Australia Pty Limited