Lilly

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28 JUN 2011
Office of Medicines Authorisation

23 June 2011

The Director
Office of Market Authorisation
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Pm-2011-01912 (PR 3002)

Dear Sir/Madam

RE: SAFETY RELATED NOTIFICATION (2011/00168R11/296668)
ACTOS® (pioglitazone hydrochloride) 15 mg, 30 mg and 45 mg tablets
(AUST R 76462, 76463 and 76464 respectively)

We hereby submit a safety related notification to update the Product Information (PI) for ACTOST® (pioglitazone hydrochloride) 15 mg, 30 mg and 45 mg blister packs (AUST R 76462, 76463 and 76464 respectively).

As per your letter of 17 June 2011 and subsequent discussion via email, the following additions have been made to the ACTOS PI:

Precautions – 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.

A five year interim analysis of a cohort of 193 099 diabetic patients ≥40 years 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 risk of bladder cancer increased with increasing cumulative dose and duration of pioglitazone use. The HR 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 HR after 24 months of pioglitazone use was 1.4 (95% CI 1.03-2.0).

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 Events Identified From Clinical Trials - 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).

Amendment of the PI by deletion of the sentence below (shown in strikethrough text) has also been included.

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.~~

Please find enclosed a copy of the revised ACTOS PI with the safety related changes highlighted in each of the updated sections. Also enclosed is a clean copy of the PI with the changes implemented.

We make our assurance that no other changes have been made to the PI and that we have in our possession, supporting data for these changes.

Please also find enclosed a credit card authorisation for $1350.00, being the processing fee for this notification.

Yours sincerely,
ELI LILLY AUSTRALIA PTY. LIMITED

[redacted]

Ph: [redacted]
Fax: [redacted]
E-mail: [redacted]

Encl.

these changes were discussed with Medical Officer (Dr Neil Mitchell) and cleared - Additional statements are acceptable for this SRN. 5/7/2011.