R11/2017481
and R12/1074136

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Re: Actos [SEC=UNCLASSIFIED]

Bronwen Harvey to [redacted] 17/06/2011 05:33 PM

Cc: Jane.Cook, Neil.Mitchell, Nick.Simpson [redacted]

[redacted]

Attached is the letter documenting our request to update the Actos PI and write a dear Health Professional letter.

Signed letter to Eli Lilly requesting changes to PI and HCP letter.pdf

Bronwen

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

[redacted]

Eli Lilly Pty Ltd
112 Wharf Road
West Ryde NSW 2114

2011/001638 R11/296668

Dear [redacted]

Actos (pioglitazone) and bladder cancer risk – request to change the Product Information and to write to health professionals

As discussed in our telephone conversation this morning, I am writing to formally request that you make amendments to the Actos Product Information (PI) to reflect the accumulated evidence of the risk of bladder cancer associated with the use of pioglitazone.

The following changes to the PI are requested and suggested text is provided for each request.

1. **Addition of a new Precaution ('Bladder Cancer') after the 'Weight Gain' Precaution and before the 'Hepatic Impairment' Precaution**

   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% 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 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 diabetes medications, and other risk factors, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to other patients was 1.2 (95% confidence interval 0.9-1.5). The risk 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).

   A retrospective cohort study using data from the French National Insurance Plan, from 1,491,060 diabetic patients ≥40 yrs of age followed for up to 4 years, found that after adjusting for age, sex and use of other diabetes medicines, the hazard ratio for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other diabetes medicines was 1.22 (CI 1.03-1.43). Exposure to pioglitazone for 12-24 months

was associated with increased risk (HR 1.34; 95% CI 1.02-1.75) as was exposure for >24 months (HR 1.36, 95% CI 1.04-1.79). A significant increase in risk was seen in males but not females.

The conclusion from these studies of an increased risk of bladder cancer with use of pioglitazone is consistent with the observation of urinary bladder tumours in rats (see 'Carcinogenicity, Mutagenicity and Impairment of Fertility').

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. The risk of bladder cancer should be considered in the care of patients treated with pioglitazone.

2. **Amendment of the Precaution regarding 'Carcinogenicity, Mutagenicity and Impairment of Fertility'**

First paragraph:

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 AUC0-24h) 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.~~

3. **Addition of information to the 'Adverse Reactions – Adverse events identified from clinical trials' section (after the 'Weight Gain' paragraph and before the 'Bone Fracture' paragraph)**

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% 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 (see 'PRECAUTIONS').

As discussed at the teleconference, the TGA is also requesting a Dear Health Professional (HP) letter which should provide information addressing:

- The changes to the PI
- The regulatory actions being undertaken by international regulatory agencies
- That the TGA and Eli Lilly are keeping the matter under review

We agreed that you would provide your draft PI changes and HP letter to the TGA on Monday 20 June 2011 with a view to having both documents finalised by Friday 24 June 2011.

Yours sincerely

Bronwen Harvey

Dr Bronwen Harvey
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Office of Product Review

17 June 2011