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Dear Healthcare Professional

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HSA's ADVISORY ON THE USE OF PIOGLITAZONE

The Health Sciences Authority (HSA) would like to update healthcare professionals on the outcome of its recent review of the benefit-risk profile of pioglitazone taking into consideration the new findings of its association with a small increased risk of bladder cancer. HSA with advice from its Pharmacovigilance Advisory Committee (PVAC) and an expert panel of endocrinologists and oncologists has assessed that the benefit-risk profile remains favourable and has put forward additional recommendations to guide doctors on its use so as to minimise the risk of bladder cancer in patients who are prescribed with the medicine. The local package insert of pioglitazone will also be amended accordingly to reflect the additional contraindications, warnings and precautions associated with its use.

2 Pioglitazone (Actos®, Takeda) has been licensed in Singapore by Invida (Singapore) Pte Ltd since 2003 for oral monotherapy in type 2 diabetes mellitus patients, particularly in overweight patients, inadequately controlled by diet and exercise and for whom metformin is inappropriate. Pioglitazone is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea.

Bladder cancer risks with pioglitazone

3 The risk of bladder cancer being associated with the use of pioglitazone was first identified in preclinical carcinogenicity studies of pioglitazone, where bladder tumours were observed in male rats receiving pioglitazone. Results from the **PRO**spective pioglit**A**zone **C**linical **T**rial In macro**V**ascular **E**vents (PROactive)* reported more bladder tumours in the pioglitazone group than the placebo group. However, this observation was not statistically significant (HR 2.96, 95% CI 0.6 to 14.7).

4 In order to address the long-term risk of bladder cancer associated with the use of pioglitazone, the US Food and Drug Administration (FDA) requested that the manufacturer of Actos® (Takeda) conduct a 10-year epidemiological study, i.e. **Kaiser Permanente Northern California (KPNC)** epidemiological study, as part of their post-market requirement.

5 In September 2010, the results from a planned 5-year interim analysis of this study became available. The KPNC epidemiological study reported a slightly elevated risk of bladder cancer with pioglitazone use (HR=1.2, 95% CI 0.9 to 1.5). The risk of bladder cancer increased slightly with increasing dose and duration of use, i.e. 30% higher among those whose duration of pioglitazone therapy was 12 to 24 months (HR 1.3; 95% CI 0.9 to 2.0) and 50% higher among those with more than 24 months of exposure (HR 1.5; 95% CI 1.1 to 2.0), as compared to non-pioglitazone users.

6 More recently in June 2011, the French Medicines Agency (Afssaps) reported that pioglitazone usage data in France suggests a small increased risk of bladder cancer (HR 1.22, 95% CI 1.05 to 1.43). The risk was noted to be increased by 75% for cumulative doses greater than or equal to 28,000 mg (HR 1.75, 95% CI 1.22 to 2.50). A significant increase in risk was also noted for treatment periods of 12 to 23 months (HR 1.34, 95% CI 1.02 to 1.75) and for treatment periods of 24 months or more (HR 1.36, 95% CI 1.04 to 1.79).

* The PROactive study, funded by Takeda Pharmaceutical Company Limited and Eli Lilly and Company, was the first prospective study evaluating the effects of an individual oral hypoglycemic agent on cardiovascular outcomes in subjects with type 2 diabetes at high cardiovascular risks. It was a 3-year study followed by a 6-year observational extension.

Regulatory Actions Taken by US FDA and the European Medicines Agency (EMA)

7 The US FDA will be strengthening the package insert of pioglitazone-containing medicines to include information on the increased risk of bladder cancer associated with using pioglitazone for more than one year. Additionally, the US FDA has advised its healthcare professionals not to prescribe pioglitazone to patients with active bladder cancer and to use it cautiously in patients with prior history of bladder cancer.

8 Following its review of this issue, EMA's Committee for Medicinal Products for Human Use (CHMP) with advice from its Scientific Advisory Group, concluded that pioglitazone containing medicines remain a valid treatment option for certain patients with type 2 diabetes despite the small increased risk of bladder cancer and that this risk could be reduced by appropriate patient selection and periodic review of the patient's treatment. The CHMP has also requested for a pan-European epidemiological study to further clarify and characterise the risk of bladder cancer associated with pioglitazone use

HSA's Assessment and Recommendations

9 From its review, HSA has assessed that the increased risk of bladder cancer associated with pioglitazone cannot be excluded. However, pioglitazone continues to be an important treatment alternative for a selected group of type 2 diabetes mellitus patients who are unable to tolerate or have inadequate response to metformin or sulfonylureas. Healthcare professionals are advised on the following risk mitigation recommendations in order to minimise the risk of development of bladder cancer in patients:

- The use of pioglitazone is contraindicated in patients with active or history of bladder cancer and in patients with uninvestigated macroscopic haematuria.
- Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. Some of the risk factors include but is not limited to the following: current or past history of smoking, family history of bladder cancer, exposure to chemicals in the workplace or to certain cancer treatments such as cyclophosphamide and radiation therapy to abdomen or pelvis.
- Bladder cancer occurs more commonly in elderly patients and in men compared to women. Caution should be exercised when pioglitazone is to be prescribed for this group of patients.
- Studies-to-date suggest that use of pioglitazone for more than a year may be associated with a small increased risk of bladder cancer.
- All patients prescribed pioglitazone should be counselled to seek medical attention if they experience blood in urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be signs and symptoms of bladder cancer.
- Physicians are advised to review the treatment of patients on pioglitazone after three to six months (and regularly thereafter) to ensure that only patients with a favourable benefit-risk profile continue treatment with pioglitazone.
- Existing patients on pioglitazone should be reviewed to ensure that benefit-risk profile remains favourable for continued use of pioglitazone.

10 Please report any serious adverse events suspected to be related to pioglitazone to HSA's Vigilance Branch at Tel: 68663538, Fax: 64786069 or report online at http://www.hsa.gov.sg/ae_online.

Thank you.

Yours sincerely



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