30th September 2011

Circular No. P08/2011

Dear Healthcare Professional,

Re: European Medicines Agency (EMA) recommends new contra-indications and warnings for pioglitazone to reduce small increased risk of bladder cancer

The EMA's Committee for Medicinal Products for Human Use (CHMP) started a European review of pioglitazone-containing medicines in March 2011 to investigate the signal of a possible increased risk of bladder cancer with pioglitazone as described in the Medicines Authority circular P07/2011. Pioglitazone containing medications are currently authorised but not marketed in Malta.

The issue of the possible risk of bladder cancer was raised at the time of marketing authorisation of the first pioglitazone-containing medicines in 2000. At that time, some preclinical studies identified cases of bladder cancer in male rats, but the evidence did not point to a risk in humans. At the time of authorisation, the company committed to perform a population-based study (KPNC) on the long-term safety of pioglitazone. The study is still ongoing and the CHMP reviewed preliminary results showing a small risk of bladder cancer in the patients treated with pioglitazone. The next signal came from a clinical trial called PROactive, where more bladder cancer cases were reported for pioglitazone than placebo. Also there has been a higher than expected number of reports of bladder cancer in patients taking pioglitazone in the EU and the United States.

The CHMP has been studying the data as they have become available and, although they are inconclusive on their own, the accumulated evidence pointed to a signal of bladder cancer that warranted a full review. The CHMP carried out this review to establish whether, in light of the evidence regarding bladder cancer, the marketing authorisations for pioglitazone-containing medicines should be maintained, varied, suspended or withdrawn across the EU.

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As the CHMP was carrying out its review, new data emerged from a population-based study in France which also pointed to a risk of bladder cancer with pioglitazone, prompting the French medicines agency to suspend the use of the medicines in France. Germany and Luxembourg took the precautionary measure of recommending that doctors not start new patients on pioglitazone while the review was ongoing.

The CHMP reviewed all available data on the occurrence of bladder cancer, including results of preclinical studies, clinical studies, epidemiological studies and spontaneous reports. The Committee also considered the advice from its Scientific Advisory Group (SAG) on Diabetes/Endocrinology. On the 21st of July 2011, the EMA finalised its review and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) confirmed that these medicines remain a valid treatment option for certain patients with type 2 diabetes but that there is a small increased risk of bladder cancer in patients taking these medicines. Evidence from different sources [2] showed that there is a small increased risk of bladder cancer. (relative risk ranging from 1.12-1.33) in diabetic patients treated with pioglitazone, in particular in patients treated for the longest durations and with the highest cumulative doses.

However, the CHMP also concluded that the small increased risk could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual patient's treatment.

What are the recommendations for prescribers?

- Prescribers are reminded that the benefits of pioglitazone continue to outweigh its risk in patients responding adequately to treatment, but that certain measures will need to be taken to reduce the risk of bladder cancer.
- Some patients will need to be taken off pioglitazone, such as those who have or have had bladder cancer or those with blood in the urine that has not yet been investigated.
- Prescribers should review the treatment of new patients and patients currently on pioglitazone after three to six months, and discontinue treatment for those who are not deriving sufficient benefit. At subsequent reviews prescribers should confirm that benefits to patients are maintained.

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- Prescribers should consider patients' risk factors for bladder cancer (such as age, smoking and exposure to certain chemicals or treatments) before starting them on pioglitazone.
- Prescribers should start elderly patients on the lowest possible dose, as they are at a higher risk of bladder cancer, as well as heart failure, with pioglitazone.
- Prescribers should use pioglitazone-containing medicines according to the updated prescribing information. The updated prescribing information also summarizes the current evidence on the risk of bladder cancer with pioglitazone.

What are the recommendations for pharmacists?

- Pharmacists should advise their patients to immediately report any blood in their urine or other symptoms of a bladder condition (such as pain while urinating or urinary urgency) to their doctor.
- Pharmacists should also inform patients who are currently on pioglitazone to have their treatments evaluated by their doctor at their next scheduled appointment. Patients with any questions should speak to their doctor.

The CHMP agreed that there is a need for further analysis of the type, evolution and severity of bladder cancer cases occurring in patients treated with pioglitazone compared to diabetics not treated with pioglitazone. It remains unclear as to whether it is an early effect or a risk with prolonged use/high cumulative dose. Therefore, the CHMP has asked the marketing authorisation holder to conduct a pan-European epidemiological study focussing on more robust characterisation of the risk, in particular the risk period and risk with increasing age, to inform the evidence-base for risk minimisation measures.

A European Commission decision on this opinion will be issued in due course.

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The Medicines Authority has participated in the discussions held at the EMA and is in agreement with the full **press release** issued by the EMA, attached here for your perusal. A **question-and-answer** document describing the outcome of this review is also available.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis

References

1. Kaiser Permanent Northern California study

2. Recently available data from epidemiological studies (Kaiser Permanente Northern California cohort study, French CNAMTS cohort study, GPRD case control study)

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