Pioglitazone and bladder cancer: PCDS statement

PCDS
Primary Care Diabetes Society

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As the committee of the Primary Care Diabetes Society (PCDS), we welcome the recent statement from the European Medicines Agency (EMA), which has reviewed pioglitazone-containing medicines following concerns over the occurrence of bladder cancer (EMA, 2011). While finding that the treatments are associated with a small increased risk of bladder cancer, the EMA concluded that they remain a valid treatment option for certain people with type 2 diabetes.

The EMA's Committee for Medicinal Products for Human Use (CHMP) reviewed all the available data on bladder cancer with pioglitazone-containing medicines, including preclinical investigations, the PROactive study (Dormandy et al, 2005), spontaneous reports and epidemiological studies (such as Lewis et al, 2011). The data collated for the EMA suggested that, while the baseline rate of bladder cancer in people with diabetes not treated with pioglitazone was 7 in 10 000, the risk in pioglitazone users increased to 15 in 10 000. These data mean there would be less than one extra case of bladder cancer per thousand people treated with pioglitazone. Set against the possible harm associated with the withdrawal of this treatment in people who have derived hypoglycaemic and cardiovascular benefit, rather than suspending the drug, the EMA has recommended new contraindications and warnings aimed at facilitating appropriate patient selection and exclusion. Changes to the summary of product characteristics for pioglitazone have since been communicated to healthcare professionals (Baum, 2011).

Pioglitazone is a member of the thiazolidinedione (TZD) "insulin sensitising" class of prescription drugs. It is available in the UK as a single agent tablet (Actos®) or in a single tablet combination with metformin (Competact®). Pioglitazone can be used alone or in combination with certain other diabetes medicines, including sulphonylureas, metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists or insulin. The licensed indications for pioglitazone should be considered carefully before commencing therapy, as should contemporary NICE and SIGN guidance on the positioning and utility of the drug.

Specifically, taking the EMA recommendations and product information changes into account, we suggest the following. When considering starting pioglitazone:

- **People with type 2 diabetes should make an informed decision about the drug, which should include a discussion on risks and benefits.**
- **These medicines should not be used in people with current, or a history of, bladder cancer, or in patients with uninvestigated haematuria. The risk factors for bladder cancer should be considered before initiating treatment with pioglitazone, particularly smoking.**
- **In people with type 2 diabetes in later life the lowest therapeutic dose should be chosen.**

When considering people with type 2 diabetes already using pioglitazone:

- **Existing users of pioglitazone who are receiving or have previously received treatment for bladder cancer, or have uninvestigated haematuria, should have their pioglitazone treatment stopped.**
- **Existing users of pioglitazone should be informed of the slightly increased risk of bladder cancer, when their medicine is reviewed, so that they can make an informed decision. We would suggest that this risk is put in the context of the possible benefit in cardiovascular risk reduction from the drug.**
- **Prescribers should review the treatment of patients on pioglitazone after 3–6 months (and regularly afterwards), to ensure that only those who are deriving sufficient benefit continue to take it.**

Importantly, long-term pioglitazone studies are ongoing, with a commitment to report at regular intervals (Takeda Pharmaceutical Company Limited, 2011). Specifically, the manufacturer of the drug has been asked to conduct a pan-European epidemiological study that will examine the risk characteristics, in particular the risk period and risk with increasing age, to inform the evidence-base for risk minimisation measures. The committee of the PCDS await the publication of these studies, and commit to keep members informed of any important emerging data or changes to prescribing information.

There are significant numbers of patients for whom pioglitazone is an effective and beneficial treatment in their struggle with type 2 diabetes. As healthcare professionals, our responsibility is to ensure that each individual is offered the treatment that is best for them, and that regular reviews ensure that any medication is only continued while it is effective. Thus, with pioglitazone we can maximise the benefits for patients while minimising any risks. ■

Baum C (2011) *Direct Healthcare Professional Communication on Pioglitazone and a Small Increased Risk of Urinary Bladder Cancer.* Takeda Pharmaceuticals Europe Limited, London. Available at: http://bit.ly/pQTvpD (accessed 05.08.2011)

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Lewis JD, Ferrara A, Peng T et al (2011) Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* **34**: 916–22

Takeda Pharmaceutical Company Limited (2011) *European Medicines Agency Recommends Revised Labeling and Guidance for Pioglitazone-Containing Products.* Takeda Pharmaceuticals Company Limited, Osaka, Japan. Available at: http://bit.ly/oqX71q (accessed 01.08.11)