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Questions and answers on the review of pioglitazone-containing medicines (Actos, Glustin, Competact, Glubrava and Tandemact)

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

The European Medicines Agency has completed a review of pioglitazone-containing medicines, following concerns over the possible risk of bladder cancer. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that, although there is a small risk of bladder cancer with pioglitazone, its benefits continue to outweigh its risks in a limited population of type 2 diabetes patients. The Committee has made recommendations to reduce the risk of bladder cancer in patients taking the medicines.

What is pioglitazone?

Pioglitazone-containing medicines are used in type 2 diabetes, a disease in which the pancreas does not make enough insulin to control the level of glucose in the blood or when the body is unable to use insulin effectively. They are available as tablets containing pioglitazone on its own (Actos and Glustin) or as tablets where pioglitazone is combined with other anti-diabetes medicines, metformin hydrochloride (Competact and Glubrava) and glimepiride (Tandemact).

Pioglitazone belongs to the class 'thiazolidinediones'. These antidiabetic substances work by attaching to receptors called 'PPAR gamma receptors' in fat, muscle and liver cells, making them more sensitive to insulin, which means that the body makes better use of the insulin it produces. As a consequence, the blood glucose is reduced and this helps to control diabetes.

Actos and Glustin were authorised in the EU in October 2000, Competact in July 2006, Tandemact in January 2007 and Glubrava in December 2007. The Marketing Authorisation Holder for these medicines is Takeda.



Why was pioglitazone reviewed?

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)¹ 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.

In a clinical trial (PROactive) more bladder cancer cases were reported for pioglitazone than placebo, and 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.

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.

What data has the CHMP reviewed?

The CHMP reviewed all the available data on the risk of bladder cancer with pioglitazone: from preclinical studies, the PROactive study and population-based studies. The Committee also considered the advice from an advisory group of experts in diabetes that also included patient representatives.

What are the conclusions of the CHMP?

The CHMP concluded that the evidence from different sources shows that there is a small risk of bladder cancer with pioglitazone. Recent data from population-based studies (the KPNC study, the French study, and a GPRD² case control study) showed a risk of bladder cancer, particularly in patients treated for the longest periods and at the highest doses.

In an analysis of several clinical trials together (a meta-analysis), 19 out of 12,506 patients taking pioglitazone had bladder cancer (0.15%) compared with 7 out of 10,212 patients not taking pioglitazone (0.07%).

The CHMP noted that there are some patients who cannot be adequately treated by other treatments and who will benefit from pioglitazone. Considering the risks associated with pioglitazone and its benefits to some patients, the CHMP concluded that the benefits outweigh the risks in those patients responding well to pioglitazone. Prescribers are advised to carefully select patients and monitor how they respond to treatment.

¹ Kaiser Permanent Northern California study

² General Practice Research Database

The CHMP also made recommendations in the prescribing information to reduce the risk of bladder cancer. These recommendations cover the monitoring of the effects of treatment, restrictions in its use and factors that prescribers and patients should take into account when using pioglitazone-containing medicines.

The Committee has agreed with the company on a letter to be sent out shortly to prescribers in the EU explaining the changes to the prescribing information.

The updated prescribing information can be found [here](#).

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.
- 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. A letter will be distributed shortly explaining what changes have been made, including advice to be given to patients. The updated prescribing information also summarizes the current evidence on the risk of bladder cancer with pioglitazone.

What are the recommendations for patients?

- Patients should 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.
- Patients currently on pioglitazone will have their treatments evaluated by their doctor at their next scheduled appointment. Patients with any questions should speak to their doctor.

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

The current European public assessment report for pioglitazone-containing medicines can be found on the Agency's website: [ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports](http://ema.europa.eu/Find%20medicine/Human%20medicines/European%20Public%20Assessment%20Reports).