U.S. Food and Drug Administration
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Drug Safety Communications

Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer

This information is an update to the FDA Drug Safety Communication: Updated drug labels for pioglitazone-containing medicines issued on August 4, 2011.

Safety Announcement

[12-12-2016] As a result of an updated review, the U.S. Food and Drug Administration (FDA) has concluded that use of the type 2 diabetes medicine pioglitazone (Actos, Actoplus Met, Actoplus Met XR, Duetact, Oseni) may be linked to an increased risk of bladder cancer. The labels of pioglitazone-containing medicines already contain warnings about this risk, and we have now approved label updates to describe the additional studies we reviewed.

We alerted the public about the possible risk of bladder cancer in September 2010 and June 2011 based on interim results from a 10-year epidemiologic study. We changed the labels of pioglitazone-containing medicines in August 2011 to include warnings about this risk, and required the manufacturer to modify and continue the 10-year study.

Pioglitazone is approved to improve blood sugar control, along with diet and exercise, in adults with type 2 diabetes. Pioglitazone works by increasing the body's sensitivity to insulin, a natural hormone that helps control blood sugar levels. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

Health care professionals should not use pioglitazone in patients with active bladder cancer, and should carefully consider the benefits and risks before using pioglitazone in patients with a history of bladder cancer.

Patients should contact their health care professionals if they experience any of the following signs or symptoms after starting pioglitazone, as these may be due to bladder cancer:

- Blood or a red color in the urine
- New or worsening urge to urinate
- Pain when urinating

We reviewed additional published studies evaluating the risk of bladder cancer in patients treated with pioglitazone. Results varied among the reviewed studies (see Data

Summary). For instance, the 10-year epidemiologic study[1] did not find an increased risk of bladder cancer with pioglitazone use, whereas another study did.[2] In addition, a randomized controlled trial found an increased risk during the trial period;[3] however the risk did not persist when patients were followed after the trial was completed.[4] Furthermore, findings of these and other reviewed studies conflicted about whether the duration of use and/or total dose over time of pioglitazone influenced the risk of bladder cancer. We also previously communicated in 2010 that bladder tumors were seen with pioglitazone exposure in animal studies. Overall, the data suggest that pioglitazone use may be linked to an increased risk of bladder cancer.

We urge patients and health care professionals to report side effects involving pioglitazone or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

We systematically reviewed published epidemiological studies evaluating the risk of bladder cancer with pioglitazone use. Some studies found an increased risk of bladder cancer with pioglitazone use and others did not. The following studies are presented to illustrate the inconsistent findings among all reviewed studies.

The manufacturer of pioglitazone, Takeda Pharmaceuticals, conducted a 10-year prospective cohort study in diabetic patients included in the Kaiser Permanente of Northern California (KPNC) database. The study included members of the KPNC diabetes registry between January 1, 1997, and December 31, 2002. The patients were followed until December 31, 2012. In June 2011, we issued a Drug Safety Communication to inform the public about the five-year interim study results, which found no significant increase in the risk for bladder cancer in patients ever exposed to pioglitazone compared to patients never exposed to pioglitazone (hazard ratio [HR]=1.2; 95% confidence interval [CI]=0.9-1.5). However, the risk of bladder cancer increased with increasing dose and duration of pioglitazone use. We have now reviewed the final 10-year results of this study.[1] The final study included a total of 158,918 patients who never took pioglitazone (never users) and 34,181 patients who had taken pioglitazone at some point (ever users). Never users were followed for an average of 8.9 years, whereas ever users were followed for an average of 6.1 years. The investigators identified 1,075 newly diagnosed cases of bladder cancer in never users and 186 cases in ever users. Ever use of pioglitazone compared to never use of pioglitazone was not associated with an increased risk for bladder cancer, with a fully adjusted HR of 1.06 (95% CI=0.89-1.26). The study also suggested a modest trend towards higher risk with increasing duration of use, but this trend was not statistically significant, which means it could have been due to chance. Compared to the interim 5-year results, these final 10-year results found weaker associations that were not statistically significant. However, the directions of the associations remained unchanged.

Between May 2001 and April 2002, the investigators for the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial enrolled type 2 diabetic patients

with extensive macrovascular disease from 18 European countries.[3] Patients were randomized to double-blind treatment with pioglitazone (n=2,605) or placebo (n=2,633), in addition to their existing antidiabetic drugs. The patients completed their final clinical trial visits between November 2004 and January 2005. The investigators conducted an observational follow-up study to investigate the occurrence of cardiovascular outcomes and malignancies after the PROactive clinical trial period ended.[4] Among 4,873 patients who completed the final PROactive trial visit, 73.9% enrolled in the observational study. Among patients who entered the follow-up study, the median total follow-up (clinical trial and observational periods) was 12.8 years. The imbalance in the number of bladder cancer cases observed in patients using pioglitazone during the clinical trial period (relative risk [RR]=2.83; 95% CI=1.02-7.85) did not persist during the combined 12.8-year period (HR=1.00; 95% CI=0.59-1.72).

Tuccori et al.[2] conducted a retrospective cohort study that assessed the association between pioglitazone use and bladder cancer. The investigators used the United Kingdom Clinical Practice Research Datalink (CPRD) to identify a cohort of patients newly treated with antidiabetic drugs between January 1, 2000, and July 31, 2013, with follow-up until July 31, 2014. There were 145,806 patients (n=10,951 initiators of pioglitazone) with a mean follow-up of 4.7 years, during which 622 patients received a diagnosis of bladder cancer. Of these, 54 developed bladder cancer after pioglitazone exposure. The fully adjusted HR for bladder cancer with pioglitazone use compared with no thiazolidinedione use was 1.63 (95% CI=1.22-2.19). Statistically significant trends in the risk of bladder cancer were observed with increasing cumulative duration of use and cumulative dose of pioglitazone.

Overall, we conclude that pioglitazone may be associated with an increased risk in urinary bladder cancer, and we have updated the drug labels to include information about these additional studies.

References

1. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015;314:265-77
2. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ 2016 Mar 30;352:i1541.
3. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.
4. Erdmann E, Harding S, Lam H, Perez A. Ten-year observational follow-up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes. Diabetes Obes Metab 2016;18:266-73.

Related Information

Pioglitazone (marketed as Actos, Actoplus Met, Duetact, and Oseni) Information

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines