U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer

Safety Announcement

[6-15-2011] The U.S. Food and Drug Administration (FDA) is informing the public that use of the diabetes medication Actos (pioglitazone) for more than one year may be associated with an increased risk of bladder cancer. Information about this risk will be added to the *Warnings and Precautions* section of the label for pioglitazone-containing medicines. The patient Medication Guide for these medicines will also be revised to include information on the risk of bladder cancer.

This safety information is based on FDA's review of data from a planned five-year interim analysis of an ongoing, ten-year epidemiological study[1], described in FDA's September 2010 ongoing safety review [1] and in the Data Summary below. The five-year results showed that although there was no overall increased risk of bladder cancer with pioglitazone use, an increased risk of bladder cancer was noted among patients with the longest exposure to pioglitazone, and in those exposed to the highest cumulative dose of pioglitazone.

FDA is also aware of a recent epidemiological study conducted in France [2] which suggests an increased risk of bladder cancer with pioglitazone. Based on the results of this study, France has suspended the use of pioglitazone and Germany has recommended not to start pioglitazone in new patients.

Facts about pioglitazone

- Sold as a single-ingredient product under the brand-name Actos. Also sold in combination with metformin (Actoplus Met, Actoplus Met XR) and glimepiride (Duetact).
- Used along with diet and exercise to improve control of blood sugar in adults with type 2 diabetes mellitus.
- From January 2010 through October 2010, approximately 2.3 million patients filled a prescription for a pioglitazone-containing product from outpatient retail pharmacies.[2]

FDA recommends that healthcare professionals should:

- Not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence.

FDA will continue to evaluate data from the ongoing ten-year epidemiological study. The Agency will also conduct a comprehensive review of the results from the French study. FDA will update the public when more information becomes available.

Additional Information for Patients

- There may be an increased chance of having bladder cancer when you take pioglitazone.
- You should not take pioglitazone if you are receiving treatment for bladder cancer.
- Tell your doctor right away if you have any of the following symptoms of bladder cancer: blood or red color in urine; urgent need to urinate or pain while urinating; pain in back or lower abdomen.
- Read the Medication Guide you get along with your pioglitazone medicine. It explains the risks associated with the use of pioglitazone.
- Talk to your healthcare professional if you have questions or concerns about pioglitazone medicines.
- Report side effects from the use of pioglitazone medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.
- Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.
- Encourage patients to read the Medication Guide they get with their pioglitazone medicine.
- Report adverse events involving pioglitazone medicines to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

To address the long-term risk of bladder cancer associated with pioglitazone use, the drug manufacturer (Takeda) is conducting a ten-year, observational cohort study as well as a nested case-control study in patients with diabetes who are members of Kaiser Permanente Northern California (KPNC) health plan.[1] Patients selected in this study had diabetes mellitus and were ≥40 years of age at study entry. Patients with bladder cancer prior to study entry or within six months of joining KPNC were excluded from this study. The cohort included 193,099 patients with diabetes.

The primary outcome of the cohort study is an incident (new) diagnosis of bladder cancer identified from the KPNC cancer registry. The primary exposure of interest is treatment with pioglitazone. Data on drug dose, duration of exposure and potential confounding factors are also obtained in the study.

A planned five-year interim analysis was performed with data collected from January 1, 1997 through April 30, 2008. The median duration of therapy among

pioglitazone-treated patients was 2 years (range 0.2-8.5 years). The results showed that after adjusting for age, sex, use of tobacco products, use of other categories of diabetes medications, and other risk factors, there was 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 to 1.5). However, the risk of bladder cancer increased with increasing dose and duration of pioglitazone use. Compared to never being exposed to pioglitazone, a duration of pioglitazone therapy longer than 12 months was associated with a 40% increase in risk (HR 1.4; 95% CI 0.9 to 2.1). The hazard ratio after more than 24 months of pioglitazone use was 1.4 (95% CI 1.03 to 2.0) and was of nominal statistical significance. Based on these data, FDA calculated that duration of therapy longer than 12 months was associated with 27.5 excess cases of bladder cancer per 100,000 person-years follow-up, compared to never use of pioglitazone.

FDA is also aware of a retrospective cohort study using data from the French National Health Insurance Plan. The study cohort included approximately 1.5 million patients with diabetes, followed for up to 4 years (2006-2009). The results showed that after adjusting for age, sex, and use of other anti-diabetic medications, there was a statistically significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents (HR 1.22; 95% CI 1.03 to 1.43). The results also showed a dose effect related to cumulative dose >28,000 mg (HR 1.75; 95% CI 1.22 to 2.5) and for exposures longer than 1 year (HR 1.34; 95% CI 1.02 to 1.75). A significant increase in risk was observed in males (HR 1.28; 95% CI 1.09 to 1.51), but not females, who experienced only a few cases. Further information is available in the European Medicines Agency (EMA) press release[3] and the Agence Française de SécuritéSanitaire des Produits de Santé (AFSSAPS) press release[4] (in French).

FDA will continue to evaluate data received from the ongoing KPNC study. The Agency will also conduct a comprehensive review of the results from the French epidemiological study. FDA will update the public when additional information becomes available.

References

1. Lewis JD, Ferrara A, PengHedderson M, Bilker WB, QuesenberryJr, et al. *Diabetes Care*. 2011;34:916-22.
2. SDI, Vector One®: Total Patient Tracker (TPT). January 2010-October 2010. Data extracted 12-15-10.

Related Information

- Agence Francaise de Securite Sanitaire des Produits de Sante (Afssaps)[5][6]
- Update on ongoing European review of pioglitazone–containing medicines[7][8]
- FDA Drug Safety Communication: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure[9] 9/17/2010
- Pioglitazone HCl (marketed as Actos, Actoplus Met, and Duetact) Information[10]

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