U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Drugs

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FDA Drug Safety Communication: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure

Safety Announcement

[09-17-2010] The U.S. Food and Drug Administration (FDA) is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether Actos (pioglitazone), is associated with an increased risk of bladder cancer. Findings from studies in animals and humans suggest this is a potential safety risk that needs further study.

Actos is used along with diet and exercise to control blood sugar or improve control of blood sugar in adults with type 2 diabetes mellitus.

Bladder cancer is estimated to occur in 20 per 100,000 persons per year in the United States and is thought to be higher in diabetics.[1]
The drug manufacturer, Takeda, has conducted a planned analysis of the study data at the five-year mark, and submitted their results to FDA. Overall, there was no statistically significant association between Actos exposure and bladder cancer risk. However, further analyses were also performed looking at how long patients were on Actos and the total amount of the drug they received during that time. An increased risk of bladder cancer was observed among patients with the longest exposure to Actos, as well as in those exposed to the highest cumulative dose of Actos.

At this time, FDA has not concluded that Actos increases the risk of bladder cancer. Its review is ongoing, and the Agency will update the public when it has additional information.

- Healthcare professionals should continue to follow the recommendations in the drug label when prescribing Actos.
- Patients should continue taking Actos unless told otherwise by their healthcare professional.
- Patients who are concerned about the possible risks associated with using Actos should talk to their healthcare professional.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety review of drugs.

Additional Information for Patients

- Do not stop taking your Actos unless told to do so by your healthcare professional.
- FDA has not concluded that Actos increases the risk of bladder cancer. The Agency is reviewing this safety concern and will update the public when additional information is available.
- Talk to your healthcare professional if you have concerns about Actos.
- Report any side effects from the use of Actos to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- FDA has not concluded that Actos increases the risk of bladder cancer. The Agency is reviewing information related to the safety concern and will update the public when additional information is available.
- Follow the recommendations in the drug label when prescribing Actos.
- Report adverse events involving Actos to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

Actos was approved July 15, 1999 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Across the approved doses Actos reduced HbA1c compared to placebo by an average of 1.5%.

In preclinical carcinogenicity studies of pioglitazone, bladder tumors were observed in male rats receiving doses of pioglitazone that produced blood drug levels equivalent to those resulting from a clinical dose. Additionally, results from two, three-year controlled clinical studies of Actos (the PROactive study[2] and a liver safety study) demonstrated a higher percentage of bladder cancer cases in patients receiving Actos versus comparators. These findings are currently included in the *Precautions--Carcinogenesis, Mutagenesis, Impairment of Fertility* section of the Actos drug label.

To further address the long-term risk of bladder cancer associated with Actos 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.[3] 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 Actos. 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 Actos-treated patients was 2 years (range 0.2-8.5 years). The study investigators did not observe a statistically significant association between any Actos exposure and increased bladder cancer risk in the study (Hazard ratio = 1.2, 95% Confidence Interval: 0.9-1.5). However, the risk of bladder cancer increased with increasing dose and duration of Actos use, reaching statistical significance after 24 months of exposure.

FDA is reviewing the data from this observational cohort study and a case control study that is nested within it, and will update the public in several months when the review is complete or earlier should additional data become available.

References

1. Seer Stat Fact Sheets: Urinary Bladder. National Cancer Institute Web site. Bethesda, MD. http://seer.cancer.gov/statfacts/html/urinb.html [1]. Accessed September 16, 2010.
2. 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.
3. Lewis JD, Ferrara A, Strom BL, Selby JV, Bilker W, Peng T, et al. The risk of bladder cancer among diabetic patients treated with pioglitazone: analysis through April 30, 2008. University of Pennsylvania and Kaiser Permanente Northern California Division of Research. Submitted to FDA, unpublished results.

Related Information

- FDA Drug Safety Podcast for Healthcare Professionals: Ongoing Safety Review of Actos (pioglitazone) and Potential Increased Risk of Bladder Cancer After Two Years Exposure [2]
- Actos (pioglitazone): Ongoing Safety Review - Potential Increased Risk of Bladder Cancer [3]
  MedWatch - 9/17/2010
- FDA reviewing preliminary safety information on Actos (pioglitazone) [4]
  FDA Note to Correspondents - 9/17/2010
- SEER Stat Fact Sheets: Urinary Bladder [5]
- Pioglitazone HCl (marketed as Actos, Actoplus Met, and Duetact) Information [6]

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1. http://seer.cancer.gov/statfacts/html/urinb.html
2. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm226749.htm
3. /Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm
4. /NewsEvents/Newsroom/PressAnnouncements/2010/ucm226244.htm
5. http://seer.cancer.gov/statfacts/html/urinb.html
6. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109136.htm
7. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
8. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

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5. http://seer.cancer.gov/statfacts/html/urinb.html
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