PIOGLITAZONE SAFETY DATA SUMMARY (initial report 6/15/11)

To address questions about 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. 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 pioglitazoone. 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 Ration[HR] 1.2, 95% Confidence Interval [CI] 0.9 to 1.5) (Now, the results of the 10 year study being conducted by the maker of Actos, Takeda Pharmaceuticals, are being submitted for publication - see below).

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 up for 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 and the Agence Francaise de SecuriteSanitaire des Produits de Sante (AFSSAPS) press release (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. (SEE THE FINAL INITIAL REPORT FROM TAKEDA PHARMACEUTICALS BELOW)

From Diabetes 2011, a Review of the 71st Annual Scientific Sessions of the American Diabetes Association in San Diego, CA. June 29, 2011:

“Just last week, another headline made its way to this discussion. It was reported by Lewis and colleagues in Diabetes Care (2011;34:916-22) that the incidence of bladder cancer may be higher in users of pioglitazone for more than 2 years. The investigators employed a database from Kaiser Permanente. Overall, there appeared to be no significant relationship, with the hazard ratio (HR) for bladder cancer in pioglitazone users at 1.2 [95% CI 0.9-1.5]). However, in those having had >24 months of therapy, there was an increased risk (1.4[1.03-2.0]).

Similarly, a recent epidemiological study by France’s health insurance agency reported 2 weeks ago concerned 1.3 million patients taking antidiabetic medications between 2006 and 2009. Of these, 155,000 persons took pioglitazone. The study found an adjusted HR of 1.33 (95% CI 1.05-1.43) for bladder cancer among those on the TZD. This report actually led to a suspension of pioglitazone sales in France, and the Germans quickly followed suit. The issue is currently under review by the European Medicines Agency (EMA), which serves as a sort of FDA for the EU.

We would point out, however, that while further study is certainly needed, the ability for any drug to cause cancer within a time frame of 2 years would be unusual. Indeed, most true carcinogens exert their effects over a period of 15-20+ years. The drug that is known to be most carcinogenic in bladder, namely cyclophosphamide, has a latency period of at least 8 years. So, the findings of Lewis and the French group may reflect unmeasured confounders. For example, since diabetes itself is associated with bladder cancer, and since pioglitazone tends to be used later on in the disease course than other medications, the investigators could be uncovering a selection bias.

Pharmacoepidemiology has an important role in initiating investigation of links between diabetes, its therapies, and cancer. ***However, results from observational studies must be interpreted with caution due to the inherent weaknesses of the data sources and the potential biases of the methods used to analyze them.*** More research with higher levels of evidence remains to be done to dissect out the complexities of the relationship between diabetes and cancer.”

2012 Update:
In the summer of 2012 at the annual scientific sessions of the ADA meetings new data from the BARI-2D Trial indicates that when compared with insulin, pioglitazone + metformin for diabetes results in ***reduced*** risk for the development of diabetic peripheral neuropathy, especially in men under the age of 50. Pioglitazone was shown to have some cardioprotective effects not seen with other antidiabetic agents in the PROactive Trial. In an abstract looking at major adverse cardiovascular events, cancer and all-cause mortality in the U.K. General Practice Research Database pioglitazone + metformin was shown to

have **SUPERIOR** outcomes compared with metformin + any other agent over a 10-year period. In a related study, although fluid retention and heart failure was increased in a study group using pioglitazone, the mortality (death) rate was not. In another study using the BARI-2D Dataset, pioglitazone + metformin (vs. Insulin + metformin) over 4.5 years showed ***reduced*** risk for peripheral vascular disease and leg amputations. Six-year data now released from the PROactive Study now indicate that the rate of bladder cancer is not statistically different comparing pioglitazone users with non-pioglitazone users. Ten year data will be published in a few more years. (IT IS NOW PUBLISHED. SEE BELOW. THIS WILL OFFICIALLY HIT THE MEDICAL LITERATURE PROBABLY SOME TIME THIS YEAR.)

Ted Tobey, M.D.
6/30/2012

2015 Update:

Takeda Announces Completion of the Post-Marketing Commitment to Submit Data to the FDA, the EMA and the PMDA for Pioglitazone Containing Medicines Including ACTOS

28.08.2014

No overall statistically significant increased risk of bladder cancer in patients ever exposed to pioglitazone in a completed 10-year epidemiological study

Osaka, Japan, August 28, 2014 – Takeda Pharmaceutical Company Limited ("Takeda") today announced the completion of the post-marketing commitment and submissions of data from a 10-year epidemiology study to regulatory authorities including the United States (U.S.) Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Japanese Ministry of Health, Labour, and Welfare (MHLW) / the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for pioglitazone containing medicines, including ACTOS (pioglitazone HCl).[1,2] This study was a 10-year epidemiology study, conducted by the University of Pennsylvania and Division of Research at Kaiser Permanente Northern California (KPNC), and was designed to investigate whether patients exposed to pioglitazone were at an increased risk of bladder cancer.[1] **Findings demonstrate that there is no statistically significant increased risk of bladder cancer among patients ever exposed to pioglitazone.[2]**

The primary analysis found no association between the use of pioglitazone and the risk of bladder cancer.[2] Additionally, no association was found between the risk of bladder cancer and the duration of pioglitazone use, increased cumulative dose of pioglitazone or the time since initiating pioglitazone.

In the five-year interim analysis published in *Diabetes Care*, a statistically significant increased risk among patients who used pioglitazone for two or more

years was observed.[1] However, the 10-year final analysis did not show any statistically significant findings of increased risk of bladder cancer with long term use of pioglitazone.[2] The data will be shared with additional regulatory authorities in accordance with local requirements around the world, and final results will be submitted for publication in 2014.

“The completion of this long-term study is a milestone in the history of pioglitazone,” said Tom Harris, head, global regulatory affairs, Takeda. “The results of the study provide reassurance with regard to the use of pioglitazone and the risk of bladder cancer and further support the positive benefit risk profile of the product.”

About Pioglitazone
Pioglitazone is approved as an agent to treat patients with Type 2 diabetes mellitus in more than 100 countries world-wide. More than 27,000 subjects have been included in clinical trials, and globally the total patient-years of exposure since first launch (1999) is estimated to be in excess of more than 29 million. Pioglitazone as a treatment of Type 2 diabetes mellitus at the recommended doses provides a valuable treatment option, and has a well established safety profile. The benefits of good glycemic control associated with Type 2 diabetes mellitus outweigh the risks associated with therapy which are appropriately communicated and managed by the current product labelling.
Pioglitazone is a thiazolidinedione for the treatment of Type 2 diabetes in adults as an adjunct to diet and exercise.

Unlike many oral antidiabetic drugs, pioglitazone is not an insulin secretagogue. Pioglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. Therefore, pioglitazone is a medication that depends on the presence of insulin for its mechanism of action, and it decreases insulin resistance in muscle and the liver, resulting in increased insulin-dependent glucose disposal as well as decreased hepatic glucose output.

Clinical studies demonstrate that pioglitazone improves insulin sensitivity in insulin-resistant patients. Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with Type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. In controlled clinical trials, pioglitazone had an additive effect on glycemic control when used in combination with sulfonylurea, metformin, or insulin.

On 12/12/16 the FDA updated its safety announcement regarding pioglitazone to conclude that pioglitazone may be linked to an increased risk of bladder cancer.

They noted that the 10-year epidemiologic study by Takeda did not find increased risk of bladder cancer, whereas another one did (Tuccori, et.al. BMJ 2016:352:i1541, who noted a relative risk of 1.63 (95% confidence interval 1.22 to 2.19)). They noted that findings conflict about whether the duration of use and/or total dose over time influences the risk of bladder cancer. They recommend that people with active bladder cancer not use pioglitazone and that people with a prior history of bladder cancer carefully evaluate the risk vs benefit of taking pioglitazone in that situation.

02/2019