

# Bladder Cancer Warning for Pioglitazone (ACTOS)

The Food and Drug Administration (FDA) announced on Aug. 4, 2011, that the product label and Medication Guide for the type 2 diabetes drug pioglitazone (ACTOS) has been revised to warn that use of the drug for more than one year may be associated with an increased risk of bladder cancer. Pioglitazone is also available in combination with metformin (ACTOPLUS MET, ACTOPLUS MET XR) and with glimepiride (DUETACT).

Pioglitazone was approved for sale in the U.S. in July 1999 and belongs to the troubled family of antidiabetic drugs known as thiazolidinediones, or glitazones. The first member of this family, troglitazone (REZULIN), was removed from the market in 2000 because of liver toxicity. Use of the other approved glitazone, rosiglitazone (AVANDIA), has recently been severely restricted because patients treated with the drug experience an elevated risk of cardiovascular events, such as heart attack and heart failure, as well as bone fractures and visual abnormalities. None of the diabetes drugs approved by the FDA has been documented to reduce the risk of heart attack or heart failure, which are major concerns for type 2 diabetes patients.

Even before the more recent evidence of bladder cancer, *Worst Pills, Best Pills News* listed pioglitazone as a "Do Not Use" drug because its many risks do not outweigh its benefits, and safer drugs, such as metformin (GLUCOPHAGE) and other older diabetes drugs like glipizide (GLUCOTROL), are available.

## Pioglitazone and bladder cancer

Before its FDA approval, pioglitazone was shown to cause urinary bladder tumors in male rats tested in a two-year (lifetime) study. To address the long-term risk of bladder cancer in people, a 10-year study



was undertaken by the manufacturer, Takeda Pharmaceutical Co. The study is still under way in patients with diabetes who are members of the Kaiser Permanente Northern California (KPNC) health plan.

Patients selected for this study had diabetes and were 40 years of age or older at the beginning of the study. Patients diagnosed with bladder cancer before the study or within six months of joining KPNC were excluded. The group totaled 193,099 patients with diabetes. Of these diabetic patients, 30,173 had used pioglitazone at some time. The remaining patients had not, even though almost all of them had used one or more of the other diabetes drugs.

The five-year interim results were reported in April 2011. Investigators found 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. Thus, the FDA calculated that the use of pioglitazone was associated with 27.5 excess cases of bladder cancer per 100,000 patients using the drug for one year compared to those who never used pioglitazone. Further evidence for bladder cancer risk has come from an epidemiological study in France, and the use of pioglitazone has been suspended there as a result of the increased risk.

Germany has recommended that no new patients start pioglitazone.

## FDA recommendations

An FDA Safety Communication recommended that health care professionals "not use pioglitazone in patients with active bladder cancer"

and that they "use pioglitazone with caution in patients with a prior history of bladder cancer."

The updated information recommends patients contact their prescribing health care professionals if they see blood or a red color in their urine or experience other symptoms such as new or worsening urinary urgency or pain when urinating after starting pioglitazone, as these may be symptoms of bladder cancer.

## New-drug fanfare overlooks harm

Despite the substantial risks associated with the use of pioglitazone and the drug's limited benefits, there were more than 11 million prescriptions dispensed in 2010, exceeding \$2.5 billion in sales.

Glitazones came onto the market with great fanfare, because they worked in a new way to control blood sugar. Often overlooked in the enthusiasm for drugs that work in unique ways is the possibility that they also present new dangers for patients. This is the case with pioglitazone and the other glitazone drugs.

## What You Can Do

If you are taking pioglitazone or a pioglitazone-containing product, you should consult your physician about switching to equally effective and safer drugs for type 2 diabetes. Exercise and diet can also be instrumental in controlling blood sugar levels.

Consumers may report serious adverse events to the FDA's MedWatch Adverse Event Reporting program:

- **Online:** [www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm](http://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm)

- **Regular mail:** Use postage-paid, pre-addressed FDA form 3500 and mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787

- **Fax:** (800) FDA-0178

- **Phone:** (800) FDA-1088 ♦