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Litigation Landscape for a Dangerous Drug Comes to a Crossroads

A look at the immediate litigation surfacing around Takeda's diabetes drug Actos, as recent studies link its long-term use in some to bladder cancer.

By Brett A. Emison

A number of scientific studies, including action from the Food and Drug Administration (FDA), linking diabetes drug Actos to bladder cancer has resulted in lawsuits filed across the country against Actos' Japanese manufacturer, Takeda. To understand what this body of litigation will look like over the coming months, it is important to bear note of what is at stake, what has happened before, and how this drug and its manufacturer have been viewed recently, in both the court of law and court of public opinion.

Recent Medical Review of the Product – The Actos Link to Bladder Cancer

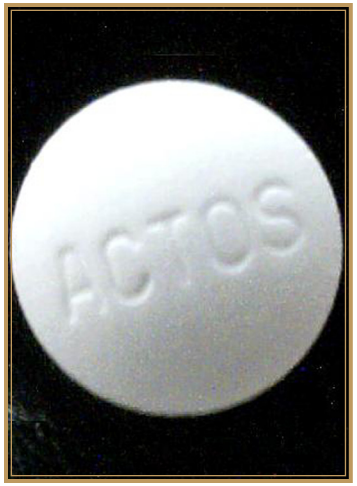
Actos, (Pioglitazone HCl) is an oral diabetes drug made by Takeda Pharmaceutical Company which was co-marketed in the United States by Eli Lilly Pharmaceuticals as Actos, Actoplus Met, and Duetact. Takeda is Japan's largest pharmaceutical corporation, with its origins dating back more than 230 years. Takeda markets its products in more than 100 countries worldwide with its U.S. subsidiaries based in Deerfield, Illinois. The manufacturer's Global Advisory Board includes key members of the international pharmaceutical industry, including members who either currently or in the past worked for such global brands as Noxxon Pharma, GlaxoSmithKline, Pfizer, Essex Woodlands Health Ventures, Bayer, Smith, and Eli Lilly.

Actos is Takeda's most successful product, representing just more than a quarter of Takeda's total revenue with total global sales of nearly $5 billion in FY2010. Sales of Actos in the Americas totaled $3.78 billion in 2010. Actos sales continue to grow and Actos sales improved nearly 12% in 2010. Takeda continues to capitalize on Actos by developing new diabetes drug based on the same Actos formulation, including Sonias (a type-2 diabetes treatment comprised of a fixed-dose of Actos and glimepiride) and Liovel (which combines NESINA and Actos). Takeda has said it "will continue efforts to obtain new prescriptions for Actos by highlighting the importance of improving insulin resistance, the main form of type 2 diabetes."

> Many people taking Actos may not realize that studies have linked prolonged use of Actos with bladder cancer.

However, despite Actos' popularity and global sales, studies have now confirmed that Actos greatly increases the risk of bladder cancer in certain patients. These studies have led to dozens of lawsuits filed across the country.

Of importance presently is a French National Health Insurance Plan investigation that showed



significant increase in the risk for bladder cancer in patients exposed to pioglitazone compared to patients exposed to other anti-diabetic agents. This study took into account adjustments for age, sex, and use of other anti-diabetic medications. (According to the French review, a cumulative dose of greater than 28,000 milligrams and an exposure of longer than one year led to a significant increase in bladder cancer, particularly in men.)

The French Medicines Agency last summer (2011) suspended use of Actos while the European Union's European Medicines Agency (EMA) completed a risk/benefit analysis of the drug. In late July 2011, the EMA confirmed an increased risk of bladder cancer, but determined that the benefit of Actos outweighed the risk for some patients and mandated a three- to six-month review of each individual patient.

Pioglitazone is also an active ingredient in the medications Actoplus Met XR, Actoplus Met and Duetact. Actos and a similar drug, Avandia, comprise a class of drugs called Thiazolidinediones, which are used to treat Type-2 diabetes. In June of 2011, the FDA released an Actos bladder cancer warning. The FDA's new warning came on the heels of an interim analysis of an epidemiological study conducted by Takeda, the Japanese pharmaceutical company that manufactures Actos.

Because the warning label was only recently changed, many people taking Actos may not realize that studies have linked prolonged use of Actos with bladder cancer. An FDA study examined a suspected link between the prolonged use of Actos and an increased risk of bladder cancer.

"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," the report states. "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."

> The longer a patient takes Actos, and/or the higher the dosage, the greater the increased risk of cancer.

A backward look at Actos' own label reveals a slow progression leading up to the current FDA warning. In 1999, as the drug was being tested, Takeda acknowledged that "(d)uring prospective evaluation…in clinical trials up to one year in duration, no new cases of bladder tumors were identified" (emphasis added). In addition, since testing had been done on animals for the drug, the product had added a caveat about the disconnect between animal testing and actual results on humans.

But in 2003, the label eliminated language that, "[t]he relationship of these findings in male rats to humans in unclear" from label. Precautions mentioned at this time were Carcinogenesis, Mutagenesis, and Impairment of Fertility. Three years later, in 2006, data from two new studies was added, as an occurrence of .44% (drug) v .14% (control) of bladder cancer was found, meaning patients taking Actos were 3 times more likely to develop bladder cancer.

Takeda is currently engaged in a ten-year observational cohort study with Kaiser Permanente Northern California, which included 193,099 Kaiser Permanente patients with diabetes. The Kaiser Permanente study showed a 30% increase in bladder cancer risk for patients taking Actos for 12-24 months and a 50% increased bladder cancer risk for patients taking Actos for 2 years or longer. The review confirmed that long-term Actos users and Actos users with the highest cumulative dose of the

drug did show an increased risk.

More than a decade after Actos was first studied, in the summer of 2011, at the request of the FDA, detailed information about Actos' link to an increased risk of bladder cancer was finally added, including a whole section on urinary bladder cancer. (Though the label also says, "There are insufficient data to determine whether pioglitazone is a tumor promoter for urinary bladder cancer.")

The FDA has now advised Actos users that taking the drug for longer than a year increases the user's risk of developing bladder cancer. The longer a patient takes Actos, and/or the higher the dosage, the greater the increased risk of cancer. The FDA also acknowledged that, after a French study pointed to an increased risk of bladder cancer, Actos had been removed from the European market pending further investigation. In July, however, the Committee for Medicinal Products for Human Use (CHMP) recommended that new labeling warning of the associated cancer risk be placed on the drug, but did not advise taking the drug off the market.

In upholding its July 2011 decision, the CHMP said that "pioglitazone remains a valid treatment option for certain patients with type 2 diabetes, when certain other treatments (metformin) have not been suitable or have failed to work adequately." In its review of pioglitazone, the CHMP noted the increased risk of bladder cancer, but said pioglitazone should be available as a second- and third-line treatment for patients who have no other options. In light of this new information, the FDA said that Actos should not be prescribed to people with bladder cancer or people with a history of bladder cancer.

In addition to the bladder cancer link, the New England Journal of Medicine also noted cardiovascular side effects caused by Actos. "There have been ongoing concerns about the safety of the diabetes drugs containing rosiglitazone (Avandia, Avandaryl, and Avandamet) — a thiazolidinedione antidiabetic

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agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus," the authors in the Journal study report. "A meta-analysis of controlled clinical trials found increases in the risk of myocardial infarction and a near-significant increased risk of death from cardiovascular causes when rosiglitazone was compared with placebo or with standard diabetes drugs."

The Journal authors summarized that the FDA is taking precautionary steps with Actos because of the agency's assessment of all available data on the cardiovascular risks of rosiglitazone. "There was no reliable evidence to refute these cardiovascular safety concerns," the agency concluded.

"After considering the data, 18 members of the advisory committee found significant cause for concern about an increase in ischemic cardiovascular events with rosiglitazone relative to other non-thiazolidinedione antidiabetic agents, whereas 6 committee members did not. Twenty-one members believed that the cardiovascular risk with rosiglitazone was significant as compared with pioglitazone. Three members did not reach this conclusion. This 21-to-3 vote also reflected recognition that available evidence on pioglitazone, including the results of a well-designed trial in high-risk patients, does not show a signal of a cardiovascular ischemic risk."

Next Steps for Litigants and Consumers

Bladder cancer is not the only risk associated with thiazolidinediones. There have been reports of health problems caused by these drugs for years. In June of 2007, the FDA issued a "black box warning" due to reports of liver and heart problems among patients taking Actos and Avandia. This warning was the result of a Cleveland Clinic study, which found that thiazolidinediones may increase a patient's risk of having a heart attack by up to 42 percent. In addition, that study found that Actos and Avandia can increase the risk for a variety of liver problems, including liver inflammation, hepatitis, elevated liver enzymes (a sign of liver damage) and liver failure. Actos and Avandia can also increase the risk of bone fractures in women.

With scores of suits now being filed against Takeda, the FDA will be monitoring the product, and a U.S. Judicial Panel dedicated to Multidistrict Litigation will decide if Actos litigation should be grouped together for pretrial case management. As consumers, the message from the FDA (as stated in their warnings written about above) is clear: patients taking Actos should consult their physician at the first sign of lower abdomen or back pain, or blood or red color in urine. Actos patients are further instructed to cease the taking of Actos if they're receiving treatment for bladder cancer.

The documented link between Actos and increased risk of bladder cancer is significant to both Takeda and patients. Bladder cancer is the fifth most common cancer in the United States while Actos has risen to be the dominant Pioglitazone-based diabetes medication with annual sales in excess of $5 billion. Millions of patients take this drug every day. Many patients, if not most, do not know of or understand Actos' link to bladder cancer. As Takeda continues to heavily market Actos, more and more patients will endure this documented side effect.

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