

THE ENDOCRINE SOCIETY
STATEMENT TO PROVIDERS ON THE SUSPENSION OF SALES OF PIOGLITAZONE
BY REGULATORY AGENCIES IN FRANCE AND GERMANY
June 13, 2011

On June 9, 2011, the French government agency that regulates prescription drugs (AFSSAPS) announced that it was suspending the sale of pioglitazone (Actos), and the German government acted similarly the following day. The rationale for removing the drug from the market was the potential increased risk of bladder cancer in patients using pioglitazone for treatment of diabetes.

The key evidence was provided by a newly-released 3-year French study of 155,000 patients taking pioglitazone and 1.3 million diabetics not on the drug. The adjusted hazard ratio for bladder cancer in this population was 1.22 (95% CL 1.05 – 1.43), with a higher risk seen among those with cumulative exposure to more than 28 grams of drug (hazard ratio = 1.75; 95% CL 1.22 – 2.50).

Another study (*Diabetes Care April 2011 34:923-929*) has also suggested a potential association between pioglitazone and bladder cancer. A five-year planned interim analysis of an ongoing 10 year U.S. study of 193,000 diabetics showed a non-significant overall hazard ratio for bladder cancer of 1.2 (95% CL 0.9 – 1.5), but the risk of bladder cancer was significant in those taking pioglitazone for two years or longer.

The drug regulatory agencies in Europe and the U.S. are continuing to evaluate the possible association between pioglitazone and bladder cancer. The Food and Drug Administration (FDA) has indicated that it is conducting an extensive examination of new data on this matter and expects to issue a statement in a few months.

In anticipation of an updated formal recommendation from the FDA in the very near future, The Endocrine Society advises patients and physicians to continue to follow the existing FDA guidance regarding pioglitazone issued nine months ago (<http://www.fda.gov/Drugs/DrugSafety/ucm226214.htm>), as outlined below:

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.*

The Society wishes to emphasize that there are many drugs that can be employed effectively to treat diabetes. Pioglitazone is currently the only readily available member of the PPAR-gamma class of drugs for diabetes treatment since the severe curtailing of the availability of rosiglitazone. In its deliberations, the FDA will need to balance the risk/benefit of pioglitazone as well as the possible consequences of having no drugs of the thiazolidinedione class available for the treatment of diabetes. In particular, the FDA's previous restriction of rosiglitazone use was predicated in part on the availability of pioglitazone as a safer alternative.

Pioglitazone is the fourth drug in the thiazolidinedione class that has demonstrated significant adverse clinical events: troglitazone (Rezulin) was associated with massive hepatic necrosis; rosiglitazone (Avandia) and muraglitazone with increased cardiovascular events; and now pioglitazone with bladder cancer. The diversity of these adverse events suggests that they might be specific effects related to the individual drug makeup rather than a class effect characteristic of all thiazolidinedione drugs. Such a conclusion makes it reasonable to continue the search for additional safe and effective drugs in this class.

The Society encourages physicians and other diabetes healthcare providers to closely monitor the ongoing release of additional information from the FDA and other sources. The Society will provide updated guidance on this topic when new information becomes available.