Closer Look

MEMORANDUM

FDA to add bladder cancer risk warning to label for pioglitazone-containing medicines - June 17, 2011

Executive Highlights

- The FDA just announced that it will be updating *Warnings and Precautions* sections of the labels and the patient medication guides for pioglitazone-containing medicines to include a warning that the use of such drugs for longer than one year could be associated with increased bladder cancer risk.

Based on its analysis of five-year interim data from a ten-year observational study investigating pioglitazone and bladder cancer risk, the FDA announced late last week that it will be updating the Warnings and Precautions sections of the labels and the patient medication guides for pioglitazone-containing medicines (Actos, ACTOplus Met, ACTOplus Met XR, Duetact) to include a warning that the use of such drugs for longer than one year could be associated with increased bladder cancer risk. In addition, the FDA is recommending for healthcare professionals not to use pioglitazone for patients with active bladder cancer or a history of bladder cancer. While the five-year interim data showed that the incidence of bladder cancer was not significantly higher for individuals treated with pioglitazone, bladder cancer risk increased with dose and duration of pioglitazone use; those who were on the medication for two or more years had higher bladder cancer risk (of nominal statistical significance) versus those who never used pioglitazone. Based on the FDA's calculations, the use of pioglitazone for longer than one year was associated with 27.5 excess cases of bladder cancer per 100,000 person-years of follow-up. For context, at the five-year mark, patients in the observational study who never used pioglitazone had a median rate of bladder cancer of 68.8 cases per 100,000 person-years, while patients treated with pioglitazone for 12-24 months had a median rate of 86.7 cases per 100,000 person-years, and patients treated with pioglitazone for more than 24 months had a median rate of 102.8 cases per 100,000 person-years (Lewis et al., Diabetes Care 2011).

In addition to continuing the evaluation of additional data from the ongoing ten-year observational study, the FDA will review the results from the French epidemiological study (see June 11, 2011 Closer Look) that led France to pull pioglitazone from the market. Meanwhile, the European Medicines Agency, which began its formal risk/benefit assessment of all available data on pioglitazone (see March 23, 2011 Closer Look), intends to review the French study at its next meeting during the week of June 20; the EMA recommends for patients on pioglitazone to continue with their current therapy in the meantime before the review is complete. For context, pioglitazone sales totaled 302.9 billion yen (~$3.5 billion) in the Americas, and 30.4 billion yen (~$350 million) in Europe in 2010.

We believe the FDA may not have made this warning its most serious ("black box") and may not be causing quite as much attention to it for a couple of reasons. First, this class is set to go generic in 2012 and they may be getting pressure from the powers that be in government not to scare people about this class. (We note this is pure speculation.) Second, it may be that because there is not another drug in the class, it may be seen as unnecessarily scary to patients to hear this news. Third, this is the only drug in the only class that addresses insulin resistance, a primary defect in type 2 diabetes, and some may not want it tarnished.

--by Vincent Wu and Kelly Close