June 11, 2011  Bale/Doneen Thoughts – Pioglitazone (Actos) and Bladder Cancer

The French drug regulatory authority (AFSSAPS) has called a halt to all formal marketing of pioglitazone (Actos) and is recommending that physicians should not prescribe any more drugs containing pioglitazone. They have made these statements based on a signal that pioglitazone may be associated with a small increase in bladder cancer in diabetics, suggesting that the risk of bladder cancer may outweigh the intended glycemic control of the drug in diabetic subjects. 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 selected in this study had diabetes mellitus and were ≥40 years of age at study entry. 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. 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 Actos-treated patients was 2 years (range 0.2-8.5 years). The study investigators did not observe a statistically significant association between any Actos exposure and increased bladder cancer risk in the study (Hazard ratio = 1.2, 95% Confidence Interval: 0.9-1.5). However, the risk of bladder cancer increased with increasing dose and duration of Actos use, reaching statistical significance after 24 months of exposure. The FDA is reviewing this data and is expected to make a formal statement in the next couple of months.

In order to fully appreciate the significance of this issue, we must first review some basic information about bladder cancer and the prevalence of bladder cancer in the general population. Bladder cancer is estimated to occur in 20 per 100,000 persons per year in the United States and is thought to be higher in diabetics. This equals 1/5000. An estimated 70,530 new cases of bladder cancer cases were diagnosed in 2010. It is more common in men than women. The most common type of bladder cancer is Urothelial carcinoma, comprising 90-95% of all bladder cancers and is strongly associated with cigarette smoking. Adenocarcinoma of the bladder comprises about 2% of all bladder cancers and is most commonly associated with prolonged inflammation and irritation. Squamous cell carcinoma comprises 1-2% of bladder cancers and is associated with longstanding stones in the bladder and chronic infection and inflammation. The prognosis of bladder cancer is determined by the stage and grade of the tumor. Low risk bladder cancer does not impact the life expectancy of the patient. High risk cancer has the potential to metastasize which will impact the life expectancy. The recent pioglitazone data does not highlight what kind of bladder cancer was increased in the diabetic patient.

Cardiovascular disease prevention often requires long term use of pharmaceutical intervention, The PROACTIVE data demonstrates that 11.3% of 2605 diabetics on Actos had a CV death, MI, stroke or ACS= 294, 13.9% of 2603 diabetics not on Actos had a CV death, MI, stroke or ACS = 361. Therefore, 66 fewer events in 2.8 years or 23 fewer events per year per approx. 5,000 diabetics occurred in the Actos arm. Comparing with bladder cancer, it is accepted that about one diabetic out of 5,000 per year will get bladder cancer regardless of glycemic
treatment. Appreciating Actos’ benefit of heart attack and stroke prevention, it would have to increase the risk of bladder cancer about 20 fold to offset the intended cardiovascular benefit.

In terms of preventing diabetes, Actos has published, randomized, prospective data showing a 72% reduced risk of developing diabetes in prediabetics (ACT NOW). We have good evidence that if a patient becomes diabetic by age 50, he or she will lose about 25-30% of their lifespan. It is known that becoming diabetic at any age will impact the quality and quantity of life. Therefore, the prognosis of bladder cancer becomes extremely pertinent. We must know the type of bladder cancer Actos may increase the risk of. At this time, we have not been informed of this. Again our conjecture is that the official agency rendering judgment on Actos is only considering its benefit as one of sugar control, as this is its only formal indication. We are in a different position because our use of Actos is for CV event and diabetes prevention. Therefore, we must weigh the risk to benefit ratio on that basis.

The best prevention of bladder cancer is to avoid smoking. People who smoke are at a three to four fold higher risk of getting this disease. Because of the recent concern with Actos increasing the risk of bladder cancer, we feel it necessary to continue to educate our patients on the risks of smoking and its link to cancer. We will specifically consider the safety of pioglitazone in our smoking patients and perhaps perform routine urine tests for the presence of hematuria, as the most common symptom of bladder cancer is blood in the urine. We also embrace this as an opportunity to educate our patients on the intended benefit and risk of their cardiovascular prevention program.

Sincerely,
Amy Doneen
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Amy Doneen and Bradley Bale