

Controversial Issues in Medicine: Pioglitazone (Actos®) and Bladder Cancer

Recent news reports have suggested that patients with diabetes who are taking pioglitazone (Actos®) may be at risk for bladder cancer. Those reports were based on a study by Lewis et al, published in the April 2011 issue of *Diabetes Care*, that found a link between long-term pioglitazone use and an increased risk of bladder cancer.¹

Reviewing the Evidence

The *Diabetes Care* article is an interim report of an ongoing 10-year study being conducted by the manufacturer of pioglitazone, Takeda, at the request of the US Food and Drug Administration (FDA). It includes 193,099 adult patients, 30,173 of whom were treated with pioglitazone. So far, study findings indicate that short-term use of the antidiabetic agent is not associated with an increased risk of bladder cancer. Pioglitazone use for greater than 12 months, however, does appear to increase bladder cancer risk in comparison to no pioglitazone use.¹ This increased risk translates into an estimated 28 extra cases of bladder cancer among pioglitazone users versus nonusers, per 100,000 person-years of follow up, according to the FDA's calculation.² A separate study, conducted in France, also revealed an association between increased bladder cancer risk and pioglitazone use.³



In response to the *Diabetes Care* interim report, the FDA updated its 2010 safety alert that informed healthcare practitioners about their review of the reported pioglitazone – bladder cancer association.⁴ Their first update, released in June 2011, alerted both the public and healthcare practitioners to the potential increased risk of bladder cancer associated with greater than 12 months of pioglitazone use. Their most recent August 2011 safety alert update states that the FDA has approved updated drug labels for pioglitazone-containing medications with new safety information describing the potential bladder cancer risk.

Study	Population	Study Period	Findings
Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study ¹	193,099 adults aged ≥ 40 years: · 30,173 exposed to pioglitazone · 162,926 unexposed	1/1/1997 – 4/30/2008	40% \uparrow risk of bladder cancer with pioglitazone use ≥ 12 months ($p_{\text{trend}}=0.03$)
Risk of bladder cancer in diabetics treated with pioglitazone in France: a cohort study using data from the SNIRAM and PMSI ²	1,491,060 adults aged 40-79 years: · 155,535 exposed to pioglitazone · 1,335,525 unexposed	2006-2009	· 22% \uparrow risk of bladder cancer with pioglitazone use ($p=0.01$) · 34% \uparrow risk with use for 12-23 months ($p=0.03$)

Guidance for Practitioners

The FDA stops short of suspending use of pioglitazone-containing medications, unlike the French Health Products Safety Agency (AFSSAPS), which took such action earlier this year.⁵

- The FDA instead recommends that healthcare practitioners use pioglitazone cautiously in patients with a history of bladder cancer and avoid use of the agent altogether in those with active bladder cancer.
- The FDA will continue to evaluate data from the ongoing 10-year study and also conduct a comprehensive review of the French study.
- The New York State Medicaid Prescriber Education Program continues to recommend metformin as a first line agent in type 2 diabetes, in combination with diet and lifestyle modifications, followed by sulfonylureas and insulin.

References:

1. Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: Interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916-922.
2. FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm>. Accessed 9/8/2011.
3. Risque de cancer de la vessie chez les personnes diabétiques traitées par pioglitazone en France : une étude de cohorte sur les données du SNIRAM et du PMSI. Available at http://www.afssaps.fr/var/afssaps_site/storage/original/application/b42a6bf9a1b63c3dbec7388d3914687b.pdf. Accessed 9/12/2011.
4. Actos (pioglitazone): Ongoing safety review-potential increased risk of bladder cancer. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm226257.htm>. Accessed 8/19/2011.
5. AFSSAPS press release. Use of medications containing pioglitazone (Actos®, Competact®) suspended. Available at http://www.afssaps.fr/var/afssaps_site/storage/original/application/4e293bcd0814c025b94d46d7502a0958.pdf. Accessed 8/19/2011.