



**Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Thiazolidinediones
-August 2017-**



Background:

The thiazolidinedione (TZD) medications were reviewed at the August 2017 National Pharmacy & Therapeutics Committee (NPTC) meeting in conjunction with other guideline-recommended second-line therapies for Type 2 diabetes mellitus (T2DM). Subsequent trials, safety reviews and meta-analyses were scrutinized to evaluate the safety and potential role of TZDs on the Indian Health Service (IHS) National Core Formulary (NCF). As a result of this review, **pioglitazone was added to the NCF.**

Discussion:

Thiazolidinediones were introduced in the 1990's as an oral insulin-sensitizing treatment for T2DM. As a class, the TZDs selectively stimulate the nuclear receptor peroxisome proliferator-activated receptor (PPAR) gamma, and to a lesser extent PPAR alpha (pioglitazone), causing an effect on insulin-sensitive genes involved in the glucose and lipid metabolism in the adipose tissue, skeletal muscle and the liver. This action reduces insulin resistance in the liver and peripheral tissues, increases utilization of insulin-dependent glucose, and decreases withdrawal of glucose from the liver. Troglitazone was the first FDA approved TZD but was removed from the market in 2000 after reports of associated drug-induced hepatitis. There are currently two FDA approved TZDs available, pioglitazone and rosiglitazone.

Historically, negative cardiovascular (CV) effects have impacted the use of TZDs, especially rosiglitazone. Beginning in 2006, multiple post-marketing studies suggested increased CV risk with rosiglitazone use, in particular a 2007 meta-analysis (published in the New England Journal of Medicine) which showed increased risk of myocardial infarction (MI) and death from CV causes¹. In 2009, findings from the RECORD trial, a manufacturer-supported CV outcomes study, demonstrated that rosiglitazone did not increase overall CV morbidity or mortality but that data were inconclusive regarding MI risk². Risk of fatal and nonfatal heart failure (HF) admission was increased with rosiglitazone (HR: 2.10, 95% CI: 1.35-3.27; $p=0.001$). The FDA restricted rosiglitazone access in 2010 and implemented a rosiglitazone Risk Evaluation and Mitigation Strategy (REMS). In 2013 however, these restrictions were lifted as was the REMS in 2015, following re-analysis of the RECORD data which found no association with rosiglitazone and increased risk of MI³.

Pioglitazone's CV effects were evaluated in the PROactive trial, a randomized, controlled trial (RCT) in T2DM patients with evidence of CV disease. The primary composite endpoint consisted of all-cause mortality, non-fatal MI, non-fatal stroke, acute coronary syndrome, coronary or leg revascularization or leg amputation. Overall, no significant difference was found between pioglitazone and placebo (HR: 0.90; 95% CI, 0.8-1.02; $p=0.095$). The trial was stopped early after a beneficial decrease in secondary endpoints (all-cause mortality, MI or stroke) was observed (HR: 0.84, 95% CI: 0.72-0.98)⁴. A meta-analysis of 19 RTCs evaluating CV outcomes in pioglitazone patients reported a statistically significant reduction in the risk of composite MI, stroke or death (HR: 0.82; 95% CI: 0.72-0.94; $p=0.005$)⁵.

Other studies have shown an increased risk of HF with rosiglitazone and pioglitazone, supported by original findings from a meta-analysis of RCTs for pioglitazone (RR: 1.32; 95% CI: 1.04-1.68; $p=0.02$) and rosiglitazone (RR: 2.18; 95% CI: 1.44-3.32; $p=0.0003$)⁶. Authors reported no increased risk of CV death however with either TZD (pooled RR: 0.93; 95% CI: 0.67-1.29, $p=0.68$). Differences in effect on lipid parameters were shown in a large RCT comparing rosiglitazone to pioglitazone. In patients taking pioglitazone, triglyceride levels were significantly decreased (-52 vs. 13 mg/dL; $p<0.001$), HDL cholesterol levels were significantly increased (5.2 vs. 2.4 mg/dL; $p<0.001$) and significantly smaller LDL cholesterol increases (12 vs. 21 mg/dL; $p<0.001$) were observed, respectively, versus those receiving rosiglitazone⁷.

The incidence of bladder cancer in association with TZDs is not evident with rosiglitazone but has been identified with pioglitazone and remains controversial. The [FDA has issued safety warnings](#) on the use of pioglitazone and recommends avoiding use in patients with active bladder cancer and suggests careful consideration prior to prescribing in patients with a history of bladder cancer. The PROactive trial demonstrated higher rates of bladder cancer in the pioglitazone arm versus the placebo arm (14 vs. 6; $p=0.069$). Additionally, two large meta-analyses observed that the incidence of bladder cancer was increased with longer duration of use and higher cumulative dose ([HR: 1.48; 95% CI: 1.09–2.00; $p=0.012$]⁸ and [RR: 1.17; 95% CI: 1.03–1.32, $p=0.013$]⁹). In 2011, the risk of bladder cancer with pioglitazone prompted the French and German Medicines Agencies to suspend the use of pioglitazone. Interestingly, the risk of bladder cancer was not shown in a 2016 European cohort study with a median duration of use of 2.8 years (HR: 1.06, 95% CI 0.89-1.26)¹⁰.

Findings:

Clinical practice guidelines support TZDs as second- or third-line options in the treatment of T2DM, with A1c reductions ranging from 1.0-1.5% depending on baseline values. Pioglitazone has been shown to improve cardiovascular outcomes (positive effects on lipid parameters), including MI and stroke. There is a demonstrated risk of non-fatal HF, weight gain and fluid retention despite no increase in HF mortality. Additionally, risk of bladder cancer has been observed in those on pioglitazone for longer durations and at higher doses, although this remains controversial. Regardless, judicious use and vigilant monitoring are required in patients with a history of bladder cancer. Current T2DM management algorithms from the [American Association of Clinical Endocrinologists / American College of Endocrinology \(end of document\)](#) and the [American Diabetes Association \(page S66\)](#) are available to help guide prescribers and weigh therapeutic options during drug initiation or adjustment.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

1. Nissen SE, Wolski K. [Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes](#). N Engl J Med. 2007;356:2457-71.
2. Home PD, Pocock SJ, Beck-Nielsen H, et al. [Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes \(RECORD\): a multicentre, randomised, open-label trial](#). Lancet 2009;373:2125-2135.
3. Mahaffey KW, Hafley G, Dickerson S, et al. [Results of a reevaluation of cardiovascular outcomes in the RECORD trial](#). Am Heart J. 2013;166 (2):240-249.
4. Dormandy JA, Charbonnel B, Eckland DJ, et al. [Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study \(PROspective pioglitAzone Clinical Trial In macroVascular Events\): a randomised controlled trial](#). Lancet 2005; 366:1279.
5. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. [Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials](#). JAMA. 2007; 298: 1180–1188.
6. Lago RM, Singh PP, Nesto RW. [Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials](#). Lancet. 2007; 370:1129–36.
7. Goldberg RB, Kendall DM, Deeg MA, et al. [A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia](#). Diabetes Care. 2005; 28:1547-54.
8. He S, Tang Y, Zhao G, et al. [Pioglitazone prescription increases risk of bladder cancer in patients with type 2 diabetes: an updated meta-analysis](#). Tumor Biol. 2014; 2095-2102.
9. Zhu Z, Shen Z, Lu Y, et al. [Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: A meta-analysis](#). Diabetes Research and Clinical Practice. 2012; 98:159-163.
10. Korhonen P, Heintjes EM, Williams R, et al. [Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries](#). BMJ. 2016;354:i3903.
11. Garber AJ, Abrahamson MJ, Barzilay JI, et al. [CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM](#). Endocr Pract. 2017; 23(2): 207-238.
12. American Diabetes Association. [Standards of Medical Care in Diabetes–2017](#). Diabetes Care. 2017; 40(1): S1-S135.