



# THE IHS PRIMARY CARE PROVIDER

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*Indian Health Service  
National Pharmacy and Therapeutics Committee  
Thiazolidinediones  
NPTC Formulary Brief  
August Meeting 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 causes<sup>1</sup>. 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 risk<sup>2</sup>. 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 MI<sup>3</sup>.

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

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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)<sup>4</sup>. A meta-analysis of 19 RCTs 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;  $p=0.005$ )<sup>5</sup>.

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;  $p=0.0003$ )<sup>6</sup>. 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 rosiglitazone<sup>7</sup>.

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;  $p=0.012$ ]<sup>8</sup> and [RR: 1.17; 95% CI: 1.03–1.32,  $p=0.013$ ]<sup>9</sup>). 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)<sup>10</sup>.

### 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.

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*Indian Health Service  
National Pharmacy and Therapeutics Committee  
GLP-1 Receptor Agonists  
NPTC Formulary Brief  
August Meeting 2017*



**Background:**

The National Pharmacy & Therapeutics Committee (NPTC) reviewed the class of glucagon-like peptide-1 receptor agonists (GLP-1 RA) at the August 2017 Summer meeting. As a result of the NPTC's clinical and pharmacoeconomic evaluation, no GLP-1 RA agents were added to the National Core Formulary (NCF).

**Discussion:**

The GLP-1 RA class includes exenatide (Byetta®), exenatide extended-release (ER) (Bydureon®), dulaglutide (Trulicity®), liraglutide (Victoza® and Saxenda®), lixisenatide (Adlyxin®) and albiglutide (Tanzeum®). In 2016, two combination products were also approved, insulin glargine/lixisenatide (Soliqua®) and insulin degludec/liraglutide (Xultophy®). The GLP-1 RA are FDA approved for the treatment of type 2 diabetes.<sup>1</sup> Endogenous GLP-1 is glucose dependent and stimulates the secretion of insulin, inhibits glucagon secretion, delays gastric emptying, promotes satiety, and increases  $\beta$ -cell growth and replication. Endogenous GLP-1 is rapidly inactivated by dipeptidyl peptidase 4 (DPP-4), however synthetic GLP-1 RA are resistant to degradation by DPP-4 which prolongs the duration (and effect) of the GLP-1 RA. The GLP-1 RA have been shown to reduce A1c by 1.0-1.5%. Benefits of GLP-1 RA include limited hypoglycemia, weight loss, potential cardiac benefit, and limited renal impairment issues.<sup>2</sup>

The Agency for Healthcare Research and Quality (AHRQ) conducted a meta-analysis of 219 studies and determined that GLP-1 RA lowered risk of hypoglycemia compared to sulfonylureas (Odds Ratio [OR] 3.1-5.3).<sup>3</sup> Metformin + GLP-1 RA also lowered the risk of hypoglycemia (OR 0.23-0.89) compared to metformin + insulin and reduced systolic blood pressure by 3mm Hg vs. metformin alone. This study also found that metformin + GLP-1 RA reduced A1c by 0.65% more than metformin + DPP-4 inhibitors. When compared to thiazolidinediones, GLP-1 RA decreased weight by an additional 2.3-3.5 kilograms. Another meta-analysis of 21 randomized controlled trials (RCT) showed that patients with a BMI of  $\geq 25$  had a mean weight loss of -2.9 kilograms (-3.6 kg to -2.2 kg) vs. controls (placebo, insulin, and oral antidiabetic medications).<sup>4</sup>

The most common adverse effects observed within this class of medications are gastrointestinal (GI) related including nausea, vomiting, and diarrhea.<sup>1</sup> The AHRQ meta-analysis concluded that GLP-1 RA had greater GI side effects compared to sulfonylureas (OR 1.4-2.4).<sup>3</sup> In the same study, metformin + GLP-1 RA had more GI effects compared to metformin + DPP-4 inhibitor (OR 1.0-7.7). The GLP-1 RA do carry a boxed warning for the risk of thyroid C-cell tumors.<sup>1</sup> Caution should also be used in patients with pancreatitis, gastroparesis, or severe GERD. However, an additional meta-analysis of RCTs observed the overall risk of pancreatitis to be small.<sup>5</sup> Of the trials examining pancreatitis risk, 32 reported no events and the remaining 9 trials reported 10 events in the GLP-1 RA group and 6 in the control group. No heterogeneity was detected in the reported cases ( $I^2 = 0.0$ ,  $p=0.53$ ; Begg's tau 0.06) and the risk of pancreatitis was not different between groups (OR 1.01 [0.37 – 2.76];  $p=0.99$ ).

Head-to-head studies of GLP-1 RA demonstrated liraglutide and dulaglutide have the largest reduction in A1c.<sup>2</sup> In terms of weight loss, liraglutide has shown the greatest reduction. Exenatide ER and lixisenatide have less GI adverse effects, but lixisenatide has less effect on weight loss compared to other agents. In a meta-analysis examining 17 RCTs, exenatide ER and liraglutide decreased A1c by 0.2% and 0.24% more than insulin glargine, respectively.<sup>6</sup> Furthermore, exenatide ER decreased A1c more than exenatide BID (Byetta®), sitagliptin and pioglitazone. It was also noted that  $\beta$ -cell function improved during treatment but did not persist after cessation.<sup>6</sup>

The most recent American Diabetes Association (ADA) guidelines recommend considering the addition of liraglutide in patients with established cardiovascular disease (CVD) and suboptimal controlled type 2 diabetes.<sup>7</sup> This recommendation was largely based off findings from *The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results: A Long Term Evaluation (LEADER)* trial, a FDA-mandated cardiovascular (CV) outcomes trial.<sup>8</sup> In the LEADER study, Type 2 diabetes patients with established CVD (~80% of patients) or at high risk who received liraglutide showed a statistically significant 13% reduction (HR 0.87; CI 95%, 0.78-0.97;  $p=0.01$  for superiority) in the primary endpoint of CV death, nonfatal myocardial infarction or nonfatal stroke. The number needed to treat was 53, over 3.8 years. When the primary endpoints were evaluated separately however, only CV death remained significant. Interestingly, results from other GLP1 RA cardiovascular outcomes trials have been inconsistent and call into question whether a class effect of CV benefit truly exists.<sup>9,10</sup>

In a 2017 meta-analysis of 113 RCTs, patients with GLP-1 RA treatment had significantly lower all-cause mortality (0.88, CI: 0.79-0.97,  $p=0.015$ ), CV mortality (0.84, CI: 0.74-0.96,  $p=0.009$ ), and overall MI (0.90, CI: 0.80-1.00,  $p=0.050$ ) compared to placebo.<sup>11</sup> No benefit was found for stroke (0.90, CI: 0.81-1.06,  $p=0.059$ ) or heart failure (0.92, CI: 0.81-1.06,  $p=0.25$ ). Several studies are underway to assess the cardiovascular effects of additional GLP-1 RA with results expected in the coming year.<sup>1,11</sup>

In addition, current guidelines by the [American Association of Clinical Endocrinologists and American College of Endocrinology](#) (AACE/ACE) recommend GLP-1 RA therapy can be considered as first-line monotherapy (if metformin is contraindicated or not tolerated) when the A1c <7.5% or with dual or triple therapy when the A1c  $\geq$ 7.5%.<sup>12</sup> Treatment with GLP-1 RA is not recommended in combination with DPP-4 inhibitors or sodium-glucose co-transporter 2 (SGLT-2) inhibitors. According to the 2017 update of the [National Institute for Health and Care Excellence \(NICE\) Guidelines on Type 2 Diabetes in Adults](#), if triple therapy (metformin and two other oral medications) is not effective, tolerated, or is contraindicated, GLP-1 RA may be considered.<sup>13</sup> Metformin with a sulfonylurea and a GLP-1 RA can be considered if the patient's BMI is  $\geq$ 35 with specific psychological or medical issues associated with obesity. It can also be considered if the patient's BMI is <35 and insulin therapy would have negative occupational implications or the patient would benefit from weight loss. The [ADA's 2017 Standards of Medical Care in Diabetes](#) recommends that GLP-1 RA may be used in dual or triple therapy when a patient's A1c is >9%.<sup>7</sup>

### Findings:

Many studies and current guidelines establish GLP-1 RA as a viable second-line treatment option in the management of type 2 diabetes. The GLP-1 RA have demonstrated significant reductions in A1c and decreased fluctuation in fasting and post-prandial glucose levels. Certain GLP-1 RA agents have shown additional benefits including reduction in mortality, reduction in cardiovascular events, improved glucose control when used in combination with basal insulin, improved blood pressure control, and weight loss. GLP-1 RA have a moderate side-effect profile including low risk of hypoglycemia, weight loss, GI issues, and low risk of pancreatitis and thyroid cancer. Pending the results of ongoing cardiovascular outcomes studies, GLP-1 RA may be considered for addition to the NCF in the future.

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