

# Wyoming Drug Utilization Review

## Type 2 Diabetes Mellitus: Thiazolidinediones

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Thiazolidinediones (TZDs), also known as glitazones, are one of the many drug classes used in the treatment of type 2 diabetes mellitus (T2DM). Troglitazone, the first TZD marketed for the treatment of T2DM, received a fast-tracked FDA approval in 1997 (2). After 3 years, troglitazone was withdrawn from the market due to at least 90 cases of liver failure linked to the medication. Seventy of those cases resulted in liver transplant or death (2). The class now contains only two medications, rosiglitazone (Avandia®) and pioglitazone (Actos®) (1). Both medications were initially approved for use in the United States in 1999 (2). Rosiglitazone is available by brand name only, and as a combination product with metformin. Pioglitazone is available in generic form, and can be found in combination products with metformin, glimepiride, and alogliptin.

TZDs are insulin sensitizing medications, lowering blood glucose by improving insulin response in target cells (1). Insulin is required for TZDs to have effect; therefore, they are not useful in the treatment of type 1 diabetes mellitus. The mechanism of action of TZDs involves the agonism of peroxisome proliferator-activated receptor gamma (PPAR-gamma). Upon activation, PPAR-gamma increases various gene products that regulate glucose and lipid metabolism (1). TZDs improve insulin response in the liver, adipose tissue, and skeletal muscle (4), subsequently reducing plasma glucose and insulin concentrations (1,3). With the use of TZD as a monotherapy, glycosylated hemoglobin (HBA1C) reductions can be expected between 0.5 to 1.4% (1,3).

First line therapy for the treatment of T2DM includes metformin and lifestyle changes (4,5).

TZDs may have a place in therapy in treatment of pre-diabetes, providing cardiovascular benefits for patients with pre-diabetes and history of stroke (4). Additionally, TZDs have been associated with reduced risk of stroke in patients with T2DM (5), and are the only relatively potent antidiabetic medication found to directly reduce insulin resistance with a low risk of hypoglycemia (4). The American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE) and the American Diabetes Association (ADA) include TZDs as an acceptable initial treatment for T2DM in instances where metformin is inappropriate or not tolerated (4,5).

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TZDs are associated with a number of adverse events and contraindications. Both medications possess a boxed warning for the use in patients with congestive heart failure (CHF) (1,3,6-9). Caution should be taken in all patients with CHF, and the drugs are contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure (1). Weight gain associated with TZDs is related to increase in both fluid retention and adipose tissue (3).

TZDs should be avoided in patients with hepatic impairment when serum transaminase levels (ALT) are more than 2.5 times the upper limit of normal (3). Serum concentrations and elimination half-life of TZDs have been found to be elevated in patients with moderate to severe liver disease (1). No changes in dosing are required for patients with renal impairment (3). Additionally, TZDs have been shown to stimulate ovulation in premenopausal anovulatory women, increasing the risk of unintentional pregnancy (1,8,9). TZDs are not recommended to be used in pregnant or lactating women due to the risk of adverse effects in the infant (1,6-9).

The use of TZDs and can increase the risk of bone fractures in both men and women (3), making them potentially inappropriate treatment options in patients already at risk for falls and/or fractures. Other common adverse events associated with TZDs include abdominal pain, back pain, diarrhea, headache, hypertension, infection, nausea, pharyngitis, and sinusitis (3,6-9). Hypoglycemia has been reported in the use of TZDs (1,3,6-9), however the risk is relatively low when compared to insulin, sulfonylureas or meglitinides (4).

Monitoring parameters of TZDs include blood glucose, A1C, liver function tests, and weight (6-9). If ALT becomes greater than 3 times the upper limit of normal, TZDs should be discontinued (3). Patients being treated with TZDs should be monitored closely for symptoms of heart failure such as sudden weight gain, edema, or difficulty breathing, and if symptoms develop, dose reduction or discontinuation should be considered (3). Those taking pioglitazone should be monitored for signs and symptoms of bladder cancer such as hematuria or dysuria (8).

Significant drug interactions with the use of TZDs are related to their metabolism by the cytochrome P450 enzyme, CYP2C8 (3). When TZDs are used with strong CYP2C8 inhibitors, such as gemfibrozil and clopidogrel, or inducers, such as rifampin, dose adjustments may be necessary. The use of TZDs with insulin potentially increases weight gain and symptoms of heart failure, while the concomitant use of rosiglitazone and insulin is not recommended due to an increased risk for myocardial ischemia. When used with nitrates, rosiglitazone has been associated with an increased risk of MI, and concurrent use is not recommended (3). Other major drug interactions with TZDs include the risk of hypoglycemia when used concurrently with sulfonylureas (6).

TZDs can be used as alternative monotherapy in patients who have failed first-line initial treatment, or as an add-on therapy in patients not meeting A1C goals with monotherapy. Treatment with TZDs is contraindicated in patients with moderate to severe heart failure or liver disease. Numerous antidiabetic treatments are available, and patient specific comorbidities and side effect profiles should be considered when selecting therapy. In general, pioglitazone is associated with fewer adverse effects and more beneficial effects.

## References:

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**The P&T Committee met for its quarterly business meeting on May 12, 2022.**

Highlights of this meeting include:

Aduhelm will be limited to indication. Diagnosis must be confirmed via PET or lumbar puncture.

Oxcarbazepine and carbamazepine will be allowed as a third-line option for treatment of neuropathic pain. A 12-week trial of a tricyclic antidepressant and a 12-week trial of a gabapentinoid will be required prior to approval.

Dartisla will be limited to indication. Tezspire and Ibsrela were referred to the Department of Health for cost analysis and PDL placement.

Adbry will require a 21 day trial of a medium AND a high potency topical steroid, and a 21 day trial of tacrolimus or pimecrolimus. Cibinqo will require the above trials as well as a 56-day trial of an approved biologic agent.

For Physician Administered Drugs, Stelara IV induction for ulcerative colitis or Crohn's disease will require a 56-day trial of the preferred agent (Humira) to mirror the criteria on the outpatient pharmacy side. Vyepti was referred to the Department of Health for cost analysis and PDL placement. Apretude, Cabenuva and Leqvio will be limited to indication.

Proposed criteria is open for public comment. Comments can be sent by email to [alewis13@uwyo.edu](mailto:alewis13@uwyo.edu). All comments should be received by July 1, 2022. The next P&T Committee meeting will be held August 11, 2022 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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June 2022  
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