

Therapeutic Class Overview

Thiazolidinediones

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (US). **Greater than** 84 million American adults have prediabetes and 90% of them do not know they have it (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations (*American Diabetes Association [ADA] Diabetes Basics, 2019*). It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (*ADA 2019*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the US (*CDC 2018*).
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, 1 or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy (*Garber et al 2019*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, or decreasing the rate of carbohydrate absorption (*Wexler 2019*).
- Pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- This review focuses on the TZDs. This class of agents enhances insulin sensitivity in adipose tissue, skeletal muscle, and the liver (*Clinical Pharmacology 2019*). There are currently 2 TZDs marketed in the US: Actos (pioglitazone) and Avandia (rosiglitazone).
- This review also includes fixed-dose combination products containing a TZD in combination with metformin, extended-release metformin, or glimepiride. An additional combination product, Oseni (alogliptin and pioglitazone), is reviewed with the DPP-4 inhibitor class. Combinations of pioglitazone/metformin, pioglitazone/metformin extended release, and pioglitazone/glimepiride are currently available. Combination rosiglitazone/metformin and rosiglitazone/glimepiride have been Food and Drug Administration (FDA) approved, but are not currently marketed.
- Re-analysis of safety data by the FDA has eliminated access restrictions to rosiglitazone-containing medications that had been in place since 2011 (*FDA press release 2015*). Restrictions were previously instituted due to the association of rosiglitazone with an increased risk of myocardial infarction (*GlaxoSmithKline [GSK] press release 2014*).
- Medispan class: Thiazolidinediones, Thiazolidinediones-Biguanide Combinations, Sulfonylurea-Thiazolidinedione Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Actos (pioglitazone)	✓
Actoplus Met (pioglitazone/metformin)	✓
Actoplus Met XR (pioglitazone/metformin extended-release)	-
Duetact (pioglitazone/glimepiride)	✓
Avandia (rosiglitazone)	-*
Avandamet (rosiglitazone/metformin) [†]	-
Avandaryl (rosiglitazone/glimepiride) [†]	-

*Generic rosiglitazone has been approved by the FDA, but it is not currently marketed.

[†]Brand Avandamet and Avandaryl have been discontinued by the manufacturer. Generic rosiglitazone/metformin and generic rosiglitazone/glimepiride have been approved by the FDA, but are not available; it is unclear whether these products will be launched in the future. Thus, at this time there is no commercially available rosiglitazone/metformin or rosiglitazone/glimepiride combination product.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	pioglitazone	pioglitazone/ metformin	pioglitazone/ glimepiride	rosiglitazone	rosiglitazone/ metformin	rosiglitazone/ glimepiride
Adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings as monotherapy or as combination therapy	✓					
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.				✓	✓	✓
Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a TZD and a sulfonylurea or who have inadequate glycemic control on a TZD alone or a sulfonylurea alone			✓			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both pioglitazone and metformin is appropriate		✓				

(Prescribing information: Actos 2017, Actoplus Met 2017, Actoplus Met XR 2017, Avandamet 2017, Avandaryl 2015, Avandia 2019, Duetact 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Data consistently demonstrate that TZDs are associated with significant lowering of glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG). Trials have demonstrated the efficacy of pioglitazone as monotherapy in treatment-naïve patients (*Russell-Jones et al 2012, Wainstein et al 2012*). Rosiglitazone (both monotherapy and in combination with metformin) has also been demonstrated to be effective in treatment-naïve patients (*Rosenstock et al 2006*).
- More frequently, TZDs have been evaluated in combination regimens in patients who failed to achieve a goal A1C with other treatment(s). In this setting, pioglitazone led to improvement in glycemic parameters when added to metformin (*Bergenstal et al 2010*), a sulfonylurea (*Hanefeld et al 2004, Kipnes et al 2001*), or an SGLT2 inhibitor (*Rosenstock et al 2012*). Rosiglitazone has also shown efficacy as add-on therapy with metformin (*Bailey et al 2005, Fonseca et al 2000, Rigby et al 2010, Scott et al 2008, Weissman et al 2005*) or a sulfonylurea (*Marre et al 2009*).
- Studies evaluating the relative A1C-lowering efficacy between TZDs and antidiabetic agents from other classes have shown varying results. In a few trials, a TZD has been shown to be less efficacious than a comparator treatment such as exenatide ER or liraglutide (*Bergenstal et al 2010, Marre et al 2009*). However, several trials have demonstrated comparable efficacy with a TZD and a comparator, such as metformin, exenatide ER, or sitagliptin (*Hanefeld et al 2004, Russell-Jones et al 2012, Scott et al 2008*). Overall A1C-lowering of TZD monotherapy is similar to metformin (*McCulloch 2017*).
- A number of trials have compared pioglitazone to rosiglitazone on various outcome measures. Most studies demonstrated no significant differences between pioglitazone and rosiglitazone for A1C, FPG, or body weight changes (*Brackenridge et al 2009, Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*). One monotherapy trial in Japanese patients (N = 373) failed to demonstrate non-inferiority of rosiglitazone to pioglitazone for changes in A1C; however, pioglitazone was associated with higher incidences of adverse events relating to edema and weight gain (*Kikuchi et al 2012*).
- In several studies pioglitazone was demonstrated to have more beneficial effects on lipid parameters compared to rosiglitazone (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- The safety of TZDs has been evaluated in several large randomized controlled trials and meta-analyses (MAs).

- An MA revealed that long-term use of TZDs was associated with a significant increased risk of fracture, which was more significant in women, compared to control (no TZD) (*Loke et al 2009*).
- An increase in the risk of non-spine fractures was reported in the ACCORD BONE trial, a longitudinal observational study. The risk of fracture among women treated with a TZD (primarily as rosiglitazone) over 1 to 2 years or > 2 years was significantly higher compared to no use (hazard ratios 2.32 and 2.01, respectively). Discontinuation of TZDs (for > 1 to 2 years) resulted in a reduced risk of fracture compared to current users and a comparable risk compared to women who never used TZDs. No significant overall effect was seen among men given TZDs (*Schwartz et al 2015*).
- An MA revealed that long-term use of TZDs was associated with a significant increased risk of any and serious pneumonia or lower respiratory tract infection compared to control (placebo, sulfonylurea, metformin) (*Singh et al 2011*).
- Pioglitazone demonstrated no increased risk of cardiovascular (CV) events (composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the leg) compared to placebo. Significantly more reports of heart failure were noted with pioglitazone; however, treatment was not associated with an increased risk of death due to heart failure (*Dormandy et al 2005, Erdmann et al 2007[b], Lincoff et al 2007*).
 - Sub-analyses of this trial revealed that patients with a prior stroke were not at an increased risk of CV events with pioglitazone, and that pioglitazone significantly decreased the risk of fatal and nonfatal myocardial infarction in patients with a previous myocardial infarction (*Erdmann et al 2007[a], Wilcox et al 2007*).
- Various MAs and interim analyses concluded that rosiglitazone may be associated with a significant increased risk of myocardial infarction (*Nissen et al 2007, Singh et al 2007*) and an insignificant increased risk of CV death (*Nissen et al 2007*) compared to control (placebo or active comparator); however, other MAs have not supported these findings (*Bach et al 2013, Home et al 2007, Lu et al 2015*). None of these analyses demonstrated an increased risk of all-cause mortality with rosiglitazone (*Home et al 2007, Lu et al 2015, Nissen et al 2007, Singh et al 2007*).
- A post-hoc analysis of BARI 2D concluded that rosiglitazone is not associated with increased rates of major adverse ischemic CV events among patients with T2DM and established CAD (*Bach et al 2013*).
- The readjudication of the RECORD safety trial performed by the Duke Clinical Research Institute (DCRI) confirmed the initial finding of the trial that rosiglitazone was not associated with an increased risk for CV events (*Mahaffey et al 2013*). However, all parties did agree that the underlying design flaws of RECORD, in particular, its open-label, non-inferiority design, mean that data from the trial will never provide definitive assurance about the safety of rosiglitazone (*Mitka 2013*). The FDA also conducted an MA to assess the CV risk associated with rosiglitazone. Overall, a statistically significant increased risk of myocardial infarction and a non-significant increased risk of major adverse CV events (MACE) were observed with rosiglitazone vs. pooled comparators. In the included placebo-controlled trials, a statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with rosiglitazone were observed; however, no increased risk of myocardial infarction or MACE was observed in the active-controlled trials (*Avandia prescribing information 2016, FDA Drug Safety Communication 2013*). Based on this data, and continued monitoring of rosiglitazone-containing products since 2013 which have not identified new pertinent safety information, the FDA announced in December 2015 that a Risk Evaluation and Mitigation Strategy (REMS) was no longer necessary to ensure the benefits of rosiglitazone-containing medicines outweigh their risks (*FDA press release 2015*).
- In several studies, pioglitazone had more favorable effects on lipid parameters compared to rosiglitazone. Rosiglitazone has been associated with significant increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and apolipoprotein B (apo B), while pioglitazone has usually been associated with neutral or favorable effects on lipid parameters (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- Two MAs concluded that pioglitazone confers a modest but clinically significant increased risk of bladder cancer and the risk is higher with increased cumulative dose or duration of exposure (*Turner et al 2014, Ferwana et al 2013*). A third MA could not exclude an association between pioglitazone exposure and bladder cancer (*Monami et al 2014*). More recently, results from cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded (*Lewis et al 2015*).

CLINICAL GUIDELINES

- Guidelines on the treatment of diabetes are available from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), the ADA, the European Association for the Study of Diabetes (EASD), and the American College of Physicians (ACP) (*ADA 2019, Garber et al 2019, Qaseem et al 2017, Davies et al 2018*).
- In the 2019 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. The ADA/EASD state that metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for treatment of T2DM. If A1C remains above target with metformin alone and the patient does not have atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. If a third agent is required to achieve glycemic goals, drug choice should be based on avoidance of adverse effects, cost, and patient preferences. There is very little trial-based evidence to guide this choice. Of note, for the first time in the ADA annual diabetes management guideline, the ADA has also aligned its recommendations with those of the American College of Cardiology (ACC) for CV risk reduction in patients with T2DM. This focuses on the use of SGLT2 inhibitors and GLP-1 agonists in appropriate patients in order to reduce adverse CV outcomes (*ADA 2019, Davies et al 2018*).
- The AACE/ACE 2019 algorithm has stratified pharmacologic recommendations for T2DM based on an A1C < 7.5%, ≥ 7.5%, and > 9%. For those entering treatment with A1C < 7.5%, monotherapy with metformin is preferred; acceptable alternatives include a GLP-1 agonist, an SGLT2 inhibitor, a DPP-4 inhibitor, or a TZD. Alpha-glucosidase inhibitors, sulfonylureas, and meglitinides may be appropriate for monotherapy in certain situations. Patients entering treatment with A1C ≥ 7.5% should be initiated on dual therapy consisting of metformin (or another first-line agent) plus a second agent. If A1C is > 9% and the patient has no symptoms, dual therapy or triple therapy should be initiated; however, symptomatic patients would derive greater benefit from the addition of insulin. At all levels of treatment, caution is advised with use of TZDs, sulfonylureas, and meglitinides. Side effects that have limited TZD use include weight gain, increased fracture risk in postmenopausal women and elderly men, and an elevated risk for chronic edema or heart failure (*Garber et al 2019*).
 - Although various MAs had pointed to a modest but clinically significant increased risk of bladder cancer with pioglitazone, a cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer (*Ferwana et al 2013, Lewis et al 2015, Monami et al 2014, Turner et al 2014*). The results from this analysis led the authors of the 2019 AACE guidelines to state that “a possible association with bladder cancer has largely been refuted” (*Garber et al 2019*). Despite this statement from the AACE guideline, the FDA states that discrepant findings from studies combined with limitations in study design and the inherent difficulty of investigating moderate effect sizes in long latency endpoints, render the totality of the evidence regarding pioglitazone and bladder cancer risk inconclusive (*Hampp et al 2017*). Therefore, the urinary bladder tumor warning remains in the pioglitazone labeling.
- The ACP recommends that clinicians prescribe metformin to patients with T2DM when pharmacologic therapy is needed. They also recommend that clinicians consider adding either a sulfonylurea, a TZD, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin when a second oral therapy is considered (*Qaseem et al 2017*).

SAFETY SUMMARY

- Contraindications:
 - Hypersensitivity to any of the components of the products.
 - Do not initiate in New York Heart Association (NYHA) Class III or IV patients.
 - For metformin containing products:
 - Do not use in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or in acute or chronic metabolic acidosis including diabetic ketoacidosis.
- Boxed warnings:
 - Pioglitazone-containing products:

- Can cause or exacerbate congestive heart failure. When initiating or increasing dose, watch for signs and symptoms. If heart failure develops, manage appropriately and either discontinue the drug or decrease the dose.
- Rosiglitazone-containing products:
 - Can cause or exacerbate congestive heart failure. When initiating or increasing dose, watch for signs and symptoms. If heart failure develops, manage appropriately and either discontinue the drug or decrease the dose.
- Metformin-containing products:
 - Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Risk factors include renal impairment, concomitant use of certain drugs, age \geq 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. If lactic acidosis is suspected, the drugs should be discontinued and general supportive measures should be instituted in a hospital setting. Prompt hemodialysis is recommended.
- Selected Warnings/Precautions:
 - Fluid retention and edema can occur.
 - Use with caution in NYHA Class I and II patients.
 - Dose-related weight gain may occur.
 - Increased risk of fractures especially in females.
 - Macular edema can occur; regular eye exams are recommended.
 - Periodic monitoring of liver enzymes is recommended.
 - Avoid metformin use in patients with hepatic disease or those using alcohol.
 - Pioglitazone may increase the risk of bladder cancer; do not use in patients with active bladder cancer and use cautiously in patients with a history of bladder cancer.
 - Hypersensitivity reactions with glimepiride have been reported, including anaphylaxis, angioedema, and Stevens - Johnson syndrome.
- Adverse effects with TZDs:
 - Edema and weight gain.
- Drug interactions with TZDs:
 - Enzyme inducers or inhibitors of CYP2C8 may affect the plasma levels of both pioglitazone and rosiglitazone.
 - Topiramate may decrease pioglitazone concentrations.
 - Patients taking concomitant colesevelam, should take pioglitazone/glimepiride or rosiglitazone/glimepiride 4 hours before colesevelam.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Actos (pioglitazone)	Tablet	Oral	Once daily. Max dose: 45 mg once daily.	Max dose is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors.
Actoplus Met (pioglitazone/metformin)	Tablet	Oral	Once or twice daily. Max dose: pioglitazone 45 mg and metformin IR 2550 mg.	Take with meals. Metformin doses > 2000 mg may be better tolerated when given 3 times a day. Avoid use in severe renal impairment (eGFR < 30 mL/min/1.73 m ²) and hepatic impairment. Initiating metformin in patients with eGFR between 30 to 45 mL/min/1.73 m ² is not recommended; however, patients who develop this level of decreased renal function while taking metformin should have the risks

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and benefits of continuing therapy assessed.
Actoplus Met XR (pioglitazone/metformin extended-release)	Tablet	Oral	Once or twice daily. Max dose: pioglitazone 45 mg and metformin ER 2000 mg.	Take with meals.
Duetact (pioglitazone/glimepiride)	Tablet	Oral	Once daily. Max dose: pioglitazone 45 mg and glimepiride 8 mg.	Take with first main meal. Max dose is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors. Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the upper limit of normal (ULN).
Avandia (rosiglitazone)	Tablet	Oral	Once or twice daily. Max dose: rosiglitazone 8 mg.	Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the ULN.
Avandamet (rosiglitazone/metformin)	Tablet	Oral	Once or twice daily. Max dose: rosiglitazone 8 mg and metformin 2000 mg.	Take with meals. Titrate gradually to reduce gastrointestinal (GI) side effects. Avoid use in severe renal impairment (eGFR < 30 mL/min/1.73 m ²) and hepatic impairment. Initiating metformin in patients with eGFR between 30 to 45 mL/min/1.73 m ² is not recommended; however, patients who develop this level of decreased renal function while taking metformin should have the risks and benefits of continuing therapy assessed.
Avandaryl (rosiglitazone/glimepiride)	Tablet	Oral	Once daily. Max dose: rosiglitazone 8 mg and glimepiride 4 mg.	Take with first main meal. Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the ULN.

See the current prescribing information for full details

CONCLUSION

- The TZDs, pioglitazone and rosiglitazone, improve glycemic control by improving insulin sensitivity. Pioglitazone and rosiglitazone are available as single-entity agents and in fixed-dose combinations with metformin or glimepiride. However, at this time there is no commercially available rosiglitazone/metformin or rosiglitazone/glimepiride combination product. Pioglitazone is also available in combination with alogliptin, which is reviewed with the DPP-4 inhibitor class of drugs.
- As monotherapy, TZDs decrease A1C by approximately 1.5%. Additional A1C-lowering can be achieved by combining a TZD with another glucose-lowering agent, such as metformin or a sulfonylurea.
- Both TZDs are associated with weight gain, and both are associated with fluid retention that can lead to or exacerbate heart failure.
- Pioglitazone and rosiglitazone have comparable effects on A1C, FPG, and body weight.

- In several studies, pioglitazone had more favorable effects on lipid parameters compared to rosiglitazone. Rosiglitazone has been associated with significant increases in total cholesterol, LDL-C, triglycerides, and apo B, while pioglitazone has usually been associated with neutral or favorable effects on lipid parameters (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- To further evaluate the issue of increased risk of myocardial infarction with rosiglitazone, an FDA Advisory Committee met in June of 2013 to review the readjudicated results from the RECORD trial. The readjudication of the RECORD safety trial performed by the DCRI confirmed the initial finding of the trial that rosiglitazone was not associated with an increased risk for CV events. However, all parties agreed that the underlying design flaws of RECORD, in particular, its open-label, non-inferiority design, mean that data from the trial will never provide definitive assurance about the safety of rosiglitazone. Previously, rosiglitazone-containing medications were available only through a restricted distribution program due to the concerns of a potential increased risk of myocardial infarction. However, changes to the REMS program based on a re-analysis of data by the FDA eliminated the access restrictions that had been in place since 2011 (*GSK press release 2014*). As of December 2015, a REMS program is no longer required for rosiglitazone-containing products (*FDA press release 2015*).
- A large RCT and an MA demonstrated that pioglitazone is not associated with an increased risk of myocardial infarction (*Dormandy et al 2005, Lincoff et al 2007*). However, both of these trials did show an increased incidence of congestive heart failure in patients taking pioglitazone.
- Two MAs concluded that pioglitazone confers a modest but clinically significant increased risk of bladder cancer, and the risk is higher with increased cumulative dose or duration of exposure (*Turner et al 2014, Ferwana et al 2013*). A third MA could not exclude an association between pioglitazone exposure and bladder cancer (*Monami et al 2014*). More recently, results from cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded (*Lewis et al 2015*). The results from this analysis led the authors of the 2019 AACE guidelines to state that “a possible association with bladder cancer has largely been refuted” (*Garber et al 2019*). Despite this statement from the AACE guideline, the FDA states that discrepant study findings, combined with limitations in study design and the inherent difficulty of investigating moderate effect sizes in long latency endpoints, render the totality of the evidence regarding pioglitazone and bladder cancer risk inconclusive (*Hampp et al 2017*). Therefore, the urinary bladder tumor warning remains in the pioglitazone labeling.
- One MA and an observational trial indicated a potential for a significantly increased risk of fracture among women treated with TZDs (*Loke et al 2009, Schwartz et al 2015*).
- Guidelines recommend metformin as first-line oral therapy for T2DM. TZDs are one of several classes of oral agents that may be used with caution in selected patients as an alternative to, or in combination with, metformin (*ADA 2019, Garber et al 2018, Qaseem et al 2017, Davies et al 2018*).

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