

Pioglitazone
Rosiglitazone

Thiazolidinediones

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Introduction

Insulin and sulfonylureas have been available for decades (since the early 1920's and the 1950's respectively)^{1,2}, and until 1995, these were the only available drug classes for patients affected by type 2 diabetes.³ Currently, 12 classes of medications are FDA-approved for treating type 2 diabetes, including biguanides (e.g. metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, amylin analogue, bromocriptine (dopamine agonist), alpha-glucosidase inhibitors, the bile acid sequestrant colesevelam, insulins, and the newly approved sodium-glucose co-transporter inhibitors (SGLT2).

The thiazolidinedione drug class (including pioglitazone and rosiglitazone) has never been far from controversy.⁴ In 2000, the first drug in this class, troglitazone, was removed from the US market due to fatal hepatic necrosis.^{5,6} Rosiglitazone concerns are related to cardiovascular adverse effects, whereas pioglitazone is about bladder cancer⁷, bone fractures and fluid retention.⁴ In the US, rosiglitazone is available only via a restricted access program developed under a risk evaluation and mitigation strategy (REMS) which was required by the FDA as of September 2010.^{5,8}

Rosiglitazone is available as a single-ingredient product (Avandia), and also in combination with other diabetes medications; with metformin (Avandamet) and with glimepiride (Avandaryl).⁸ No generic rosiglitazone is available yet and the earliest that it could become available would be 2015 (several patents listed).⁹ Rosiglitazone is an insulin sensitizer and is used to treat patients with type 2 diabetes associated with insulin resistance. It stimulates glucose uptake in skeletal muscle and adipose tissue and lowers plasma insulin levels.⁵

Pioglitazone is available as a single-active product (Actos), and in combination with other diabetes medications; with alogliptin (Oseni), with glimepiride (Duetact), and with metformin (Actoplus Met). In the last year, pioglitazone has become available as generic in the US costing about 18-38 times less than the brand (Actos).¹⁰ Pioglitazone lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It is a potent and selective agonist for peroxisome proliferator-activated receptor-gamma (PPARgamma) which is abundant in the cells within the renal collecting tubules. Therefore, fluid retention results from stimulation by thiazolidinediones which increases sodium reabsorption.¹¹

Table 1. FDA-approved thiazolidinedione products ¹²

Note: Rosiglitazone generics not yet available

Drug Name	Active Ingredients
Pioglitazone	
ACTOPLUS MET	METFORMIN HYDROCHLORIDE; PIOGLITAZONE HYDROCHLORIDE
ACTOPLUS MET XR	METFORMIN HYDROCHLORIDE; PIOGLITAZONE HYDROCHLORIDE
ACTOS	PIOGLITAZONE HYDROCHLORIDE
DUETACT	GLIMEPIRIDE; PIOGLITAZONE HYDROCHLORIDE
OSENI	ALOGLIPTIN BENZOATE; PIOGLITAZONE HYDROCHLORIDE
PIOGLITAZONE	PIOGLITAZONE HYDROCHLORIDE
PIOGLITAZONE HYDROCHLORIDE	PIOGLITAZONE HYDROCHLORIDE
PIOGLITAZONE HYDROCHLORIDE AND GLIMEPIRIDE	GLIMEPIRIDE; PIOGLITAZONE HYDROCHLORIDE
PIOGLITAZONE HYDROCHLORIDE AND METFORMIN HYDROCHLORIDE	METFORMIN HYDROCHLORIDE; PIOGLITAZONE HYDROCHLORIDE
Rosiglitazone	
AVANDAMET	METFORMIN HYDROCHLORIDE; ROSIGLITAZONE MALEATE
AVANDARYL	GLIMEPIRIDE; ROSIGLITAZONE MALEATE
AVANDIA	ROSIGLITAZONE MALEATE
ROSIGLITAZONE	ROSIGLITAZONE MALEATE
ROSIGLITAZONE MALEATE	ROSIGLITAZONE MALEATE
ROSIGLITAZONE MALEATE; GLIMEPIRIDE	ROSIGLITAZONE MALEATE; GLIMEPIRIDE
ROSIGLITAZONE MALEATE; METFORMIN HYDROCHLORIDE	ROSIGLITAZONE MALEATE; METFORMIN HYDROCHLORIDE

Type 2 anti-diabetic medications

Type 1 diabetics require insulin treatment due to a lack of insulin. Type 2 diabetes mellitus (T2DM) involves cellular insulin resistance. Therefore, the mechanism of actions of the medications for type 2 diabetes include stimulating insulin release, decreasing absorption or hepatic production of glucose, and improving insulin sensitivity of target organs.¹³ Oral agents become less effective as beta cell function declines and it may be necessary to add an injectable medication such as insulin (or to switch to insulin) to manage blood sugar levels.¹⁴

Table 2. Comparison of Antidiabetic Agents¹⁵⁻²⁵

Class	Agents in class	Route of administration	Mechanism of action	Labeled Indications	Notable Adverse Effects / Limiting Acceptability ²⁵⁻²⁸
Alpha-glucosidase Inhibitors (AG-i)	Acarbose Miglitol	Oral tablets	Lower postprandial glucose. Competitive inhibitor of alpha-glucosidase (gut enzyme), resulting in delayed breakdowns of complex carbohydrates, thus delaying polysaccharide absorption.	Adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes mellitus	Bloating, flatulence, diarrhea
Amylin Mimetics	Pramlintide	Injectable solution; subcutaneous	Synthetic analog of human amylin which works by prolonging gastric emptying (leading to feeling of early satiety), reduces postprandial glucagon secretion, and centrally-mediate appetite suppression	Adjunctive treatment with mealtime insulin in Type 1 diabetes mellitus Adjunctive treatment with mealtime insulin in Type 2 diabetes mellitus, with or without concurrent sulfonylurea and/or metformin	Nausea, hypoglycemia
Biguanides	Metformin Metformin/Alogliptin Metformin/Glipizide Metformin/Glyburide Metformin/Linagliptin Metformin/Pioglitazone Metformin/Repaglinide Metformin/Rosiglitazone Metformin/Saxagliptin Metformin/Sitagliptin	Oral tablets	Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity in muscle and fat	First-line management of Type 2 diabetes mellitus <u>Unlabeled Indications:</u> Gestational diabetes mellitus (GDM); polycystic ovary syndrome (PCOS); prevention of Type 2 diabetes mellitus	Nausea, lactic acidosis, Vitamin B12 deficiency
Bile acid sequestrant	Colesevelam	Oral tablets	Unknown; may reduce glucose absorption, may reduce hepatic insulin resistance (reduction in hepatic glucose production), may affect mediators of glucose metabolism	Type 2 diabetes (combination therapy with insulin or oral antidiabetic agents) Dyslipidemia	GI intolerance (nausea, bloating, constipation), increased triglycerides
Dipeptidyl peptidase IV Inhibitors (DPP-4-i)	Alogliptin Alogliptin/Metformin Alogliptin/Pioglitazone Linagliptin Linagliptin/Metformin Saxagliptin Saxagliptin/Metformin Sitagliptin Sitagliptin/Metformin Sitagliptin/Simvastatin	Oral tablets	Inhibits dipeptidyl peptidase IV (DPP-IV) enzyme resulting in prolonged active incretin levels resulting in increased insulin synthesis & release and decreased glucagon secretion	Management of Type 2 diabetes mellitus as an adjunct to diet and exercise as monotherapy or in combination with other antidiabetic agents	Pancreatitis
Dopamine Agonist	Bromocriptine=> Cycloset®	Oral tablets	Mechanism of action is unknown in type 2 diabetes. Believed to affect circadian rhythms (reversal of insulin resistance and decreases in glucose production, without increasing serum insulin concentrations) mediated in part by dopaminergic activity.	Management of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise	Nausea, orthostasis

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists	Exenatide Liraglutide	Injectable solution; subcutaneous	Analogues of the hormone incretin which increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, increase B-cell growth/replication, slow gastric emptying, and decrease food intake	Treatment of Type 2 diabetes mellitus *May also improve hypertension in patients with diabetes	Headache, nausea, diarrhea. May be associated with pancreatitis, renal insufficiency, and thyroid cell cancer in rodents (Victoza)
Insulins	Rapid-acting Aspart: Novolog Glulisine: Apidra Lispro: Humalog Short-acting Regular: Humulin, Humulin R, Novolin Intermediate-acting NPH: Humulin N, Novolin N Intermediate to Long-acting Detemir Long-acting Glargine Combination Products Aspart protamine + Aspart Lispro protamine + Lispro NPH + Regular: Humulin 70/30, Novolin 70/30	Injectable solution; subcutaneous, intravenous	Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs for insulin include the liver, skeletal muscle, and adipose tissue	Treatment of Type 1 diabetes mellitus and Type 2 diabetes mellitus to improve glycemic control	Weight gain, hypoglycemia
Meglitinides (GLN)	Nateglinide Repaglinide Repaglinide/Metformin	Oral tablets	Phenylalanine derivatives which stimulate insulin release and reduce postprandial hyperglycemia	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or a thiazolidinedione	Hypoglycemia (rare), slight increases in serum uric acid, dizziness
Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitor	Canagliflozin	Oral tablets	Inhibits sodium-glucose co-transporter 2 (SGLT2) in the proximal renal tubules=>reduces reabsorption of filtered glucose from the tubular lumen and lowers the renal threshold for glucose (RT _G). SGLT2 is the main site of filtered glucose reabsorption. It results in increased urinary excretion of glucose, thereby reducing plasma glucose concentrations.	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Urinary tract and genital infections (fungal), increased urination, may increase LDL

Sulfonylureas (SU)	Chlorpropamide Glimepiride Glimepiride/Pioglitazone Glimepiride/Rosiglitazone Glipizide Glipizide/Metformin Glyburide Glyburide/Metformin Tolazamide Tolbutamide	Oral tablets	Stimulates insulin release, reduces glucose output and increases insulin sensitivity	Management of Type 2 diabetes mellitus as monotherapy or in combination with metformin or insulin	Hypoglycemia
Thiazolidinediones (TZD)	Pioglitazone Pioglitazone/Alogliptin Pioglitazone/Glimepiride Pioglitazone/Metformin Rosiglitazone Rosiglitazone/Glimepiride Rosiglitazone/Metformin	Oral tablets	Agonists for peroxisome proliferator-activated receptor-gamma (PPARgamma) which influences the production of a number of gene products involved in glucose and lipid metabolism; improves insulin sensitivity	Management of Type 2 diabetes mellitus as monotherapy or in combination with a sulfonylurea, metformin, or sulfonylurea plus metformin	Weight gain, fluid retention (may contribute to heart failure), fracture risk, increased risk of bladder cancer (pioglitazone), increased risk of cardiovascular adverse effects (rosiglitazone)

Thiazolidinediones

Table 3. Uses, FDA approval date and REMS/Black Box Warning^{29,30}

Treatment	Labeled indication	Unlabeled indication	FDA Approval	REMS and Black Box Warning
Pioglitazone (Actos)	Diabetes mellitus type 2	<ul style="list-style-type: none"> • Cerebrovascular disease - Impaired glucose • Diabetes mellitus type 2 - Disorder of cardiovascular system, Secondary disease; Prophylaxis • Diabetes mellitus type 2 - Disorder of cardiovascular system; Prophylaxis • Diabetic nephropathy, In Type 2 Diabetes • Generalized atherosclerosis • Polycystic ovary syndrome • Restenotic lesion of coronary artery; Prophylaxis 	07/15/1999	<p>Pioglitazone hydrochloride may cause or worsen congestive heart failure. Monitor patients for signs and symptoms of heart failure after initiation or dose increases. Should such signs and symptoms of congestive heart failure develop, manage according to current standards of care and consider discontinuing therapy or a dose reduction. Pioglitazone hydrochloride is not recommended in patients with symptomatic heart failure and is contraindicated in patients with established NYHA Class III or IV heart failure.</p> <p>⇒ FDA approved a REMS (to ensure benefits outweigh the risks). However, FDA later rescinded REMS requirements.</p> <p>See the FDA REMS page: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm</p>

Treatment	Labeled indication	Unlabeled indication	FDA Approval	REMS and Black Box Warning
Rosiglitazone (Avandia) (Avandamet) (Avandaryl)	Diabetes mellitus type 2	<ul style="list-style-type: none"> • Coronary stent stenosis • Diabetes mellitus; Prophylaxis • Polycystic ovary syndrome • Restenotic lesion of coronary artery; Prophylaxis 	05/25/1999	<p>May cause or worsen congestive heart failure, is not recommended in patients with symptomatic heart failure, and is contraindicated in patients with established NYHA class III or IV heart failure. Monitor patients for signs and symptoms of heart failure after initiation or dose increases and if heart failure occurs, consider dose reducing or discontinuing rosiglitazone maleate and manage according to current standards of care. A meta-analysis of 52 clinical trials (mean duration 6 months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with a statistically significantly increased risk of myocardial infarction.</p> <p>⇒ Available only through a restricted distribution program: AVANDIA-Rosiglitazone Medicines Access Program (prescribers and patients need to enroll)</p> <p>REMS & Medication guide http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337552.pdf</p>

Table 4. Usual and Maximum Doses for Thiazolidinediones³⁰⁻³²

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling/Lexicomp	Maximal Recommended Dose	FDA/DEA Classification
Pioglitazone (Actos)	Yes	Oral tablet: 15 mg 30 mg 45 mg	<p>Initiate ACTOS at 15 mg or 30 mg once daily. Limit initial dose to 15 mg once daily in patients with NYHA Class I or II heart failure. If there is inadequate glycemic control, the dose can be increased in 15 mg increments up to a maximum of 45 mg once daily.</p> <p>Obtain liver tests before starting ACTOS. If abnormal, use caution when treating with ACTOS, investigate the probable cause, treat (if possible) and follow appropriately. Monitoring liver tests while on ACTOS is not recommended in patients without liver disease.</p>	<p>Monotherapy or combination: 45 mg daily.</p> <p>Patients taking strong CYP2C8 inhibitors (e.g., gemfibrozil): 15 mg once daily.</p>	Rx only

Drug	Generic	Dosage Form(s)	Usual Dose from Product Labeling/Lexicomp	Maximal Recommended Dose	FDA/DEA Classification
Rosiglitazone (Avandia)	No	Oral tablet: 2 mg 4 mg 8 mg	Start at 4 mg daily in single or divided doses; do not exceed 8 mg daily. Dose increases should be accompanied by careful monitoring for adverse events related to fluid retention. Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels.	Monotherapy: 8 mg daily. Fixed-combination with metformin: 8 mg of rosiglitazone and 2 g of metformin daily. Fixed-combination with glimepiride: 8 mg of rosiglitazone and 4 mg of glimepiride daily.	Rx only

Clinical Guidelines

⇒ Table 6 contains summary information from different guidelines.



Lifestyle optimization is the first step in management of type 2 diabetes, but often pharmacotherapy is needed.^{27,33} Metformin remains the cornerstone of type 2 anti-diabetic treatment. Advantages of metformin include low risk of hypoglycemia, can promote modest weight loss, it has a robust cardiovascular safety profile, and low cost.²⁵ If metformin alone is inadequate, the guidelines include various options as add-on therapy with a focus on individualized goals of treatment.

The American Diabetes Association (**ADA**) and European Association for the Study of Diabetes (**EASD**) released a position statement in **April 2012** which differed from previous published documents.²⁷ The new position statement focused on a patient-centered approach by selecting second and third-line drugs on individually-tailored basis. The position statement was not designed to be an algorithm, but rather to encourage physicians to critically evaluate the risk-to-benefit ratio for each patient.³⁴ Metformin remains the first-line pharmacotherapy. The new position statement listed five different choices as add-on therapy to metformin treatment, and other drugs not shown may be used in selected patients.²⁷ The new position statement includes a summary table of the available glucose-lowering agents including information on advantages, disadvantages and cost as well as general recommendations.²⁷ Considerations to guide the choice of pharmacological agents include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences.”³⁵

Examples of add-on drugs based on specific patient needs or concerns could include³⁴:

Reduced cost: Sulfonylureas or insulin

Weight loss desired: GLP-1 or DPP-4 inhibitor

Hypoglycemia avoidance: Thiazolidinediones, GLP-1 receptor agonists or DPP-4 inhibitors

The general recommendations (ADA/EASD position statement²⁷) state that other drugs not shown (alpha-glucosidase inhibitors: Acarbose, miglitol; bile acid sequestrant: colesevelam; dopamine agonists:

bromocriptine; amylin mimetics: pramlintide) may be used in selected patients but they have modest efficacy and/or limiting side-effects.

Table 5. Summary table adapted from the ADA/EASD position statement ²⁷

	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	GLP-1 receptor agonist	Insulin
Efficacy	high	high	intermediate	high	highest
Hypoglycemia	moderate risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	gain
Major Side-effects	hypoglycemia	edema, HF, fractures, ? MI (rosiglitazone) ? bladder cancer (pioglitazone)	Rare Urticarial/angioedema ? pancreatitis	GI ? Acute pancreatitis C-cell hyperplasia/ medullary thyroid tumors in animals	hypoglycemia

The American Association of Clinical Endocrinologists (AACE) also issued new guidelines and the **new 2013 AACE Comprehensive Diabetes Management Algorithm** replaces the 2009 AACE/ American College of Endocrinology (ACE) Diabetes Algorithm for Glycemic Control. Their glycemic control algorithm lists drugs in a specific order which is a suggested hierarchy of usage.³³ It is also recommended that treatment be individualized based on attributes specific to patients and medications themselves. All FDA-approved medications are included in this algorithm making it the most comprehensive and updated guideline and it stratifies choice of therapies based on initial A1C level.²⁵ After metformin, GLP-1 receptor agonists are recommended as preferred agents due to its robust efficacy and weight loss and its low hypoglycemic risk. The **Global guidelines**³⁶ include sulfonylureas as a second choice. Sulfonylureas do not require special injectable instructions and may be more readily available in some settings (lower cost). They have also been used for many years and therefore have a long-term safety profile. However, they are associated with hypoglycemia, modest weight gain (which would make it a less desirable option in patients who would benefit from weight loss) and they lack durability.³³

The National Institute for Health and Care Excellence (**NICE**) **guidelines** Type 2 diabetes (NICE clinical guideline 66) and Type 2 diabetes: newer agents (NICE clinical guideline 87) are currently in the process of being updated.³⁷ The current NICE guidelines also recommend metformin as first-line and to consider a sulfonylurea as a second option (if metformin is contraindicated) or to be added to metformin if necessary (if not overweight; if a rapid therapeutic response is required due to hyperglycaemic symptoms). DPP-4 inhibitors (referring to sitagliptin) and thiazolidinediones (referring to pioglitazone) can be added as triple therapy, but it is recommended to only continue treatment with these medications if the reduction in HbA1c is at least 0.5% in 6 months and the benefits and risks have been weighed and discussed with the patient.³⁸

When might a DPP-4 inhibitor be preferable to a TZD? ³⁸	When might a TZD be preferable to a DPP-4 inhibitor? ³⁸
<ul style="list-style-type: none"> • TZD is contraindicated • Further weight gain would cause significant problems • Poor response to or did not tolerate TZD in the past 	<ul style="list-style-type: none"> • DPP-4 is contraindicated • Patient has marked insulin insensitivity • Poor response to or did not tolerate DPP-4 in the past

Exenatide is included in this NICE guideline 87 as an option to be added to metformin and a sulfonylurea if insulin is not acceptable or if the BMI ≥ 35 kg/m², but should only be continued if the patient has a reduction in HbA1c of at least 1% and a reduction of weight of $\geq 3\%$ of initial body weight in 6 months.³⁸ Acarbose is included as an option for patients who are unable to use other glucose-lowering medications.³⁸

Special populations with different individual circumstances require different choices in therapy. For example, patients with kidney disease may need an alternative to metformin (due to the risk of lactic acidosis). The

AACE guidelines also mention that metformin be used with caution in patients with alcoholism or extremes of age (existing creatinine cutoffs may not be applicable), and that the risk of vitamin B12 deficiency is higher with metformin use (may decrease absorption long-term).^{25,39} Long-acting metformin formulations may reduce gastrointestinal side-effects (nausea & diarrhea) in some metformin intolerant patients and it may also be of benefit in patients who prefer once-daily dosing (Immediate-release metformin has a short half-life and should be taken 2-3 times per day). Extended-release metformin and combination tablets also reduce pill-burden which is associated with improved persistence and adherence.²⁵

ADA Standards of Medical Care in Diabetes 2013³⁵

First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
Metformin	Another oral agent (e.g. sulfonylurea, TZD, DPP-4 inhibitor); GLP-1 agonist; Basal insulin	Patient-centered approach: Efficacy; Cost; Potential Side effects; Effects on weight; Comorbidities; Hypoglycemia; Risk; patient preferences	Readers are referred to the ADA/EASD position statement.	Consider insulin with/without additional agents from outset in newly diagnosed with markedly symptomatic and/or elevated blood glucose levels or A1C. Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

Table 6. Current Guidelines

Guideline	First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
ADA/EASD²⁷ 2012	Metformin	Another oral agent (e.g. sulfonylurea/glinide ^c , TZD, DPP-4 inhibitor); GLP-1 agonist; Basal insulin	Efficacy; Adverse effect profile; Cost; Injection preference; Patient preferences, needs and values; Glucose issue (fasting or prandial); dosing flexibility; Age; Weight; Chronic kidney disease	Same as for dual therapy; Insulin most likely to obtain A1c goal; Strongly consider if A1c≥8.5%	At diagnosis with significant hyperglycemic symptoms and/or dramatically elevated glucose > 300-350 mg/dL or A1c≥10%-12%
ACCE²⁵ 2013	Metformin ^f (alternative in suggested order: GLP-1 agonist, DPP-4-i, AG-I, SGL-2, TZD, SU/GLN)	In suggested order: GLP-1 agonist, DPP-4-i, TZD, SGLT-2, basal insulin, colesevelam, bromocriptine QR, AG-I, sulfonylurea/GLN	Individualized A1c target; Patient attributes (age, co-morbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, life expectancy, etc.); Medication attributes (risk of inducing hypoglycemia, weight gain, ease of use, cost, safety impact of kidney, heart or liver disease).	In suggested order: GLP-1 agonist, TZD, SGLT-2, basal insulin, DPP-4-i, colesevelam, bromocriptine QR, AG-I, sulfonylurea/GLN	Symptomatic patients (polyuria & weight loss) with entry A1c > 9%. Patients receiving 2 oral agents or GLP-1 with A1C >8% (or not at goal).
NICE³⁸	Metformin	Sulfonylurea; DPP-4 inhibitor or TZD (if high risk for hypoglycemia); GLP-1 agonist (if BMI ≥35 kg/m ² ; if BMI lower & insulin unacceptable)	Risk of hypoglycemia Problem with weight gain Patient preference (occupational implications, social, recreational, or other issues e.g. with insulin)	DPP-4 inhibitor (refers to sitagliptin or vildagliptin), TZD (refers to pioglitazone) or GLP agonist Or Insulin (particularly with marked hyperglycemia)	A1c remains ≥7.5% despite other measures

Guideline	First-line monotherapy ^a	Dual therapy ^b (options to add to metformin)	Considerations based on:	Triple Therapy (options to add to metformin)	When to initiate insulin
ACP ⁴⁰	Metformin	No specific recommendation provided	No specific recommendation provided	Not addressed	Not addressed
Global Guideline for Type 2 Diabetes³⁶ 2012	Metformin ^d (unless contraindicated e.g. renal impairment)	Sulfonylurea (usual approach), and other medications are included as alternative approaches ^e	Availability; Cost; Efficacy; Side-effects; Effect on weight; Hypoglycemia risk; Long-term outcomes	Insulin or an oral agent (DPP-4, TZD, or Alpha-glucosidase inhibitor) as the usual approach for a third-line agent and GLP-1 agonists as an alternative approach	At triple therapy stage (if diabetes control remains unsatisfactory, the usual approach includes a third oral agent or insulin), but it may be considered earlier too.

^a If metformin is contraindicated, drugs from other classes (figure 2, position statement)²⁷ such as sulfonylureas can be used as first-line therapy. A shorter-duration sulfonylurea, such as glipizide is less likely to cause hypoglycemia than the older, long-acting sulfonylureas).^{41,42} Other alternatives include thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists or repaglinide (particularly in patients with chronic kidney disease at risk for hypoglycemia).^{27,36,42}

^b Rapid-acting secretagogues (meglitinides) may be used in place of sulfonylureas. It should be considered in patients with irregular meal schedules or who develop postprandial hypoglycemia on sulfonylureas. Meglitinides may be associated with less hypoglycemia, but requires more frequent dosing.²⁷

^c If non-insulin monotherapy at maximum tolerated dose do not achieve or maintain the A1C target over 3-6 months.⁴³

^d The alternative approach is a sulfonylurea or an alpha-glucosidase inhibitor.³⁶

^e The alternative approach is metformin (if not first line) or alpha-glucosidase inhibitor or DPP-4 inhibitor or TZD.

^f Upon diagnosis, monotherapy is recommended if A1C <7.5%, dual therapy if A1C 7.5% to 9%, and insulin if A1C >9%. If the treatment goal of <6.5% is not met within 3 months, AACE/ACE recommends intensifying therapy by adding another agent from a different class (dual therapy). SGLT-2 is based upon phase 3 clinical trial data.

Clinical Efficacy

According to the AACE 2013 guidelines, for patients with recent-onset T2DM and those with mild hyperglycemia (<7.5%), lifestyle modification and metformin monotherapy (1500 – 2000 mg/day) is generally sufficient and most patients will achieve their glycemic goal.²⁵ In March 2011, the Agency for Healthcare Research and Quality (AHRQ) published an updated review (including metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors, GLP-1 agonists as monotherapy and combination therapy). They reported that a high strength of evidence showed that most medications were similarly efficacious at lowering A1C by about 1% compared with baseline values (apart from the DPP-4 inhibitors which did not lower A1C to the same extent as metformin monotherapy), and by another 1% when added to monotherapy.³

Table 7. Efficacy, and kidney disease^{25,27}

Medication	Efficacy	A1C lowering	Kidney Disease ^{25,44,45}
Alpha-glucosidase inhibitors	lower ²⁷ / modest A1C lowering ³³	0.4-0.7% ^{25,46} 0.5-1% ^{27,28}	Not recommended in CKD (specifically if serum creatinine >2 mg/dL).
Amylin Mimetics	Lower or equivalent overall A1C lowering vs. other therapies ²⁷	0.5-1% ²⁶	Pramlintide: Clcr >20 mL/minute: No dosage adjustment necessary. Clcr ≤20 mL/minute & dialysis: No dosage adjustment provided in manufacturer's labeling (has not been studied). ⁴⁷ Not recommended if CKD stage 4 or greater ⁴⁸
Biguanide (Metformin)	Compares favorably to other therapies ³³ ; high ²⁷	1-1.5% ^{25,27,49}	Contraindicated if serum creatinine level ≥1.4 mg/dL in women and ≥1.5 mg/dL in men and in patients with abnormal clearance
Bromocriptine	lower ²⁷ / slight glucose lowering ³³	0.5% ^{25,50} 0.5-1% ²⁷	No dose adjustment; predominantly metabolized in liver; use with caution in CKD (no studies in patients with reduced GFR) ⁴⁸
Colesevelam	lower ²⁷ / modest glucose lowering ³³	0.4-0.6% ^{25,51} 0.5-1% ²⁷	No dose adjustment
DPP-4 Inhibitor	lower ²⁷ / intermediate/modest A1C lowering ³³	0.5-0.9% ^{25,52,53} 0.5-1% ²⁷	Linagliptin – predominantly non-renal elimination – no dose adjustment. Most DPP-4 inhibitors require dose adjustment (excreted by kidney).
GLP-1 agonist	high ²⁷ /robust A1C lowering ³³	0.8-2.0% ^{25,54} 1-1.5% ²⁷	Liraglutide => not excreted via kidney => no restrictions in CKD (but not tested in end-stage renal disease/kidney transplant patients). Exenatide should be used with caution in stage 3 CKD and avoided if CrCl <30mL/min.
Insulin	highest	1.5-3.5% ²⁶	May increase risk of hypoglycemia; dosage adjustment (insulin requirements may be reduced) & monitoring may be necessary ⁵⁵
Meglitinides	reduced A1C lowering ^{27,33} Repaglinide more effective than nateglinide	0.5-1% ²⁷	Repaglinide: adjust dose in severe renal impairment (Cl _{cr} 20-40 mL/min); not studied Cl _{cr} <20 mL/min or hemodialysis Nateglinide: No dose adjustments; dialysis => reduced medication exposure and plasma protein binding. Severe renal dysfunction => more susceptible to glucose-lowering effect; use with caution. ⁴⁴
SGLT-2 (Canagliflozin)	Clinicians have little experience ³³	0.45-0.92% ²⁵ 0.7-1% ²⁸	eGFR 45-<60 mL/min/1.73 m ² : Maximum 100 mg once daily. Not recommended if eGFR 30-45 mL/min/1.73 m ² ; contraindicated if eGFR <30 mL/minute/1.73 m ² & ESRD receiving hemodialysis

Sulfonylurea	high ²⁷ / relatively potent A1C lowering ³³	0.4-1.2% ²⁵ 1-1.5% ²⁷	All excreted renally => lower starting doses. Use with caution as hypoglycemia risk may be higher (due to higher blood levels and prolonged half-life in CKD)
TZD	high ²⁷ / relatively potent A1C lowering ³³	0.7-1.2% ^{25,56} 1-1.5% ²⁷	Pioglitazone => not excreted renally => no dose adjustment Rosiglitazone => no dosage adjustment ⁵⁷ Caution: risk of fluid retention & heart failure – avoid in patients with advanced kidney failure (especially if they have preexisting heart failure) ⁵⁸

Table 8. AHRQ updated 2011 review

First-line monotherapy	Dual therapy (options to add to metformin)	Considerations based on:	Triple Therapy, insulin, and future research
<p>Evidence supports: metformin; most medications similarly efficacious at lowering hemoglobin A1C by about 1% (compared with baseline values); exception: DPP-4 inhibitor class did not lower A1c to the same extent as metformin when used as monotherapy; evidence still sparse regarding long-term outcomes and the comparative efficacy of the oral medications; metformin more favorable effect on body weight; Metformin decreased low-density lipoprotein cholesterol (LDL-C) relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors.</p>	<p>Combination therapies could decrease A1c levels more than monotherapies; addition of most oral medications to monotherapy further improved glycemic control by lowering A1C by another 1% (compared to baseline values); two-drug combinations compared with each other demonstrated similar reductions in A1c</p>	<p>Weight gain: oral metformin and injectable GLP-1 agonists not associated with weight gain. Greatest risks of mild-to moderate hypoglycemia: sulfonylureas and 2-drug combinations (sulfonylureas had a 4-fold higher risk of mild-to-moderate hypoglycemia compared with metformin alone, and, in combination with metformin, had more than a 5-fold increased risk compared with metformin plus a thiazolidinedione). Increased risk for heart failure and cardiovascular events: Thiazolidinediones (relative to sulfonylureas). Increased risk for hip and nonhip fractures: Thiazolidinediones (relative to metformin). Gastrointestinal upset: Metformin (compared with TZD users). Macrovascular and microvascular outcomes: low strength and insufficient evidence apart from metformin which was associated with lower all-cause mortality and cardiovascular-disease mortality. CHF - low strength evidence: higher risk for combination therapy with rosiglitazone (compared to metformin+sulfonylurea) and moderate strength evidence: higher risk for TZD monotherapy (compared to sulfonylurea)</p>	<p>Future research should strive to include triple combination regimens. Studies of the addition of basal or premixed insulin compared to metformin or TZDs are lacking</p>

Safety and adverse effects

Appendix 1 contains information on the most common and serious adverse effects that have been reported in the product labels for rosiglitazone and pioglitazone.

The new AACE Comprehensive Diabetes Management Algorithm (2013) include metformin, GLP-1 agonists, DPP-4 inhibitors, alpha-glucosidase inhibitors, colesevelam, and bromocriptine as medication options with few adverse effects or possible benefits. Caution is recommended with the use of SGLT-2, TZD, SU/GLN, and basal insulin.²⁵

Refer to the “Profiles of Antidiabetic Medications” slide (PPT->[AACE Comprehensive Diabetes Management Algorithm – 2013](#)) for a visual comparison of the different medications in terms of their safety impact or risk of causing hypoglycemia, weight gain, renal/GU disease and effects, GI effects, congestive heart failure, cerebrovascular disease, and bone loss.³³

Table 9. TZD profile adapted from the ADA/EASD position statement²⁷, AACE algorithm²⁵

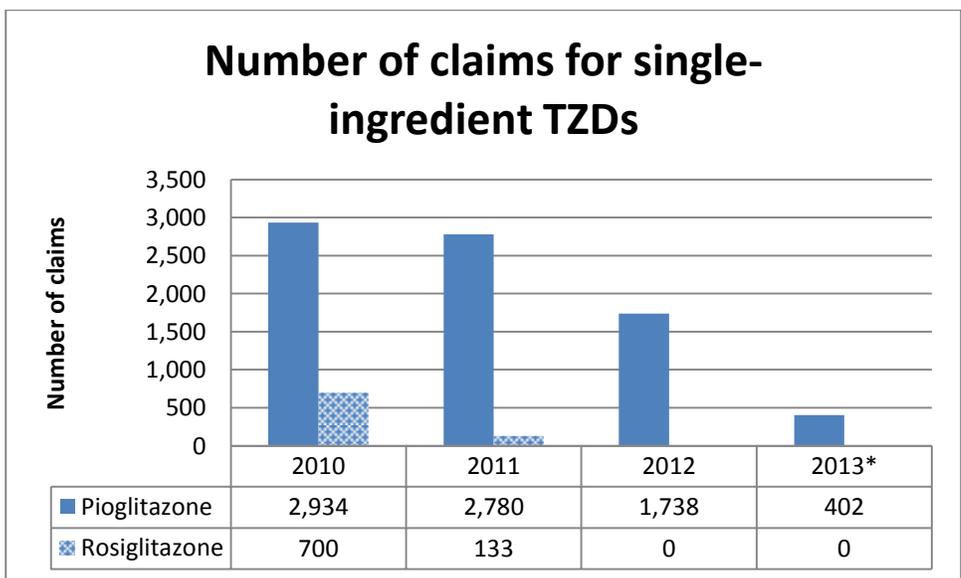
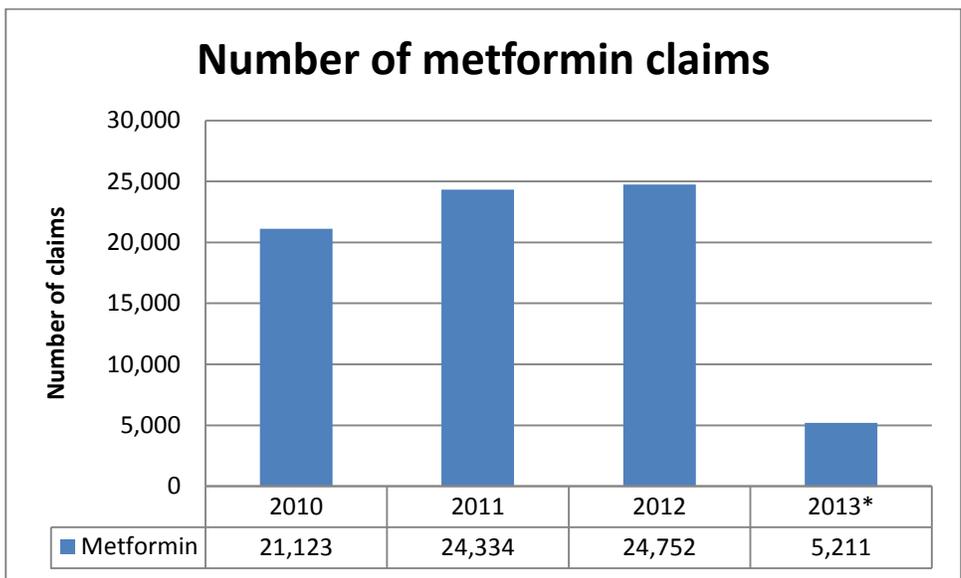
Medication attributes	ADA/EASD	AACE
Hypoglycemia	Low risk/no hypoglycemia	Neutral
Weight	Gain	Gain
Renal/GU	Edema, ? bladder cancer (pioglitazone)	May worsen fluid retention
Heart	CHF ? MI (rosiglitazone)	CHF: Moderate CVD: Neutral
GI	-	GI Sx: Neutral
Bone	Fractures	Moderate Bone Loss

The Avandia (rosiglitazone) drug label states that it is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus after consultation with a healthcare professional who has considered and advised the patient of the risks and benefits and either are (1) already taking Avandia, or (2) not already taking Avandia and are unable to achieve adequate glycemic control on other diabetes medications, and, in consultation with their healthcare provider, have decided not to take pioglitazone (Actos) for medical reasons. Avandia should not be used in patients with type 1 diabetes mellitus, for the treatment of diabetic ketoacidosis, and coadministration of Avandia and insulin is not recommended.⁵⁹

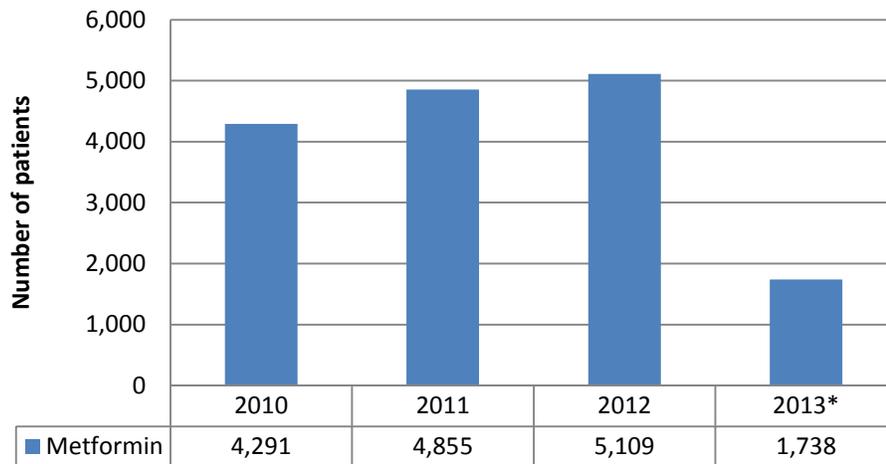
In August 2011, the FDA issued a statement that they have approved updated drug labels for pioglitazone-containing medicines to include safety information that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer.⁶⁰ The FDA's review included data from a planned five-year interim analysis of an ongoing, ten-year epidemiological study which showed that although there was no overall increased risk of bladder cancer with pioglitazone use, an increased risk of bladder cancer was noted among patients with the longest exposure to pioglitazone, and in those exposed to the highest cumulative dose of pioglitazone.^{61,62} The FDA was also aware of the epidemiological study in France that suggested an increased risk of bladder cancer with pioglitazone.^{62,63} “The updated drug labels recommend that healthcare professionals should: Not use pioglitazone in patients with active bladder cancer. Use pioglitazone with caution in patients with a prior history of bladder cancer.”⁶⁰ “The updated drug labels recommend that patients should: Contact their healthcare professional if they experience any sign of blood in the urine or a red color in the urine or other symptoms such as new or worsening urinary urgency or pain on urination since starting pioglitazone, as these may be due to bladder cancer.”⁶⁰

On May 31, 2012, results of a nested case-control study were published in the *British Medical Journal* that pioglitazone is associated with an increased risk for incident bladder cancer among persons with type 2 diabetes (doubled in patients treated with pioglitazone for 2 years or more).⁶⁴ This additional evidence reinforces the FDA warning, and clinicians and patients should weigh carefully the benefits and risks of using this drug.

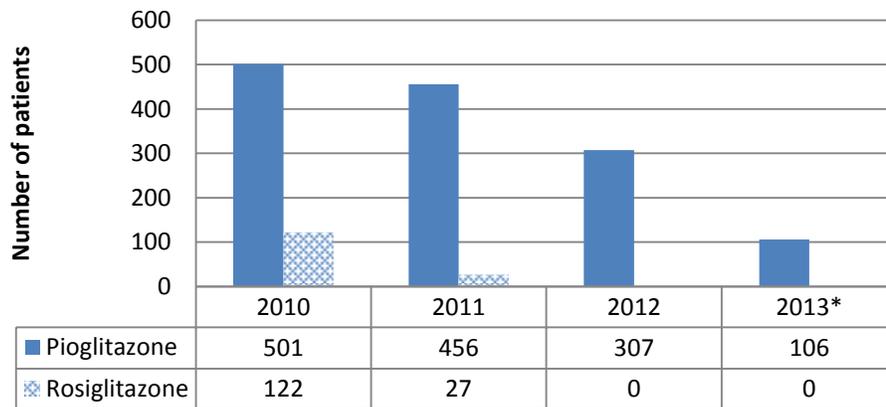
Utah Medicaid Utilization Data



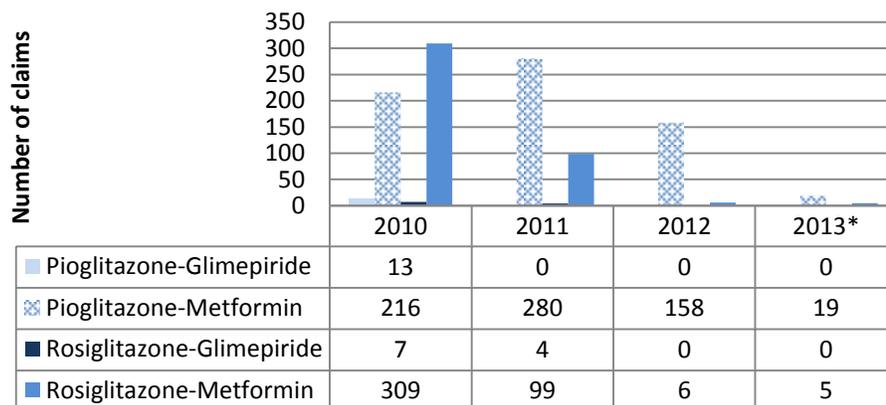
Number of patients on metformin



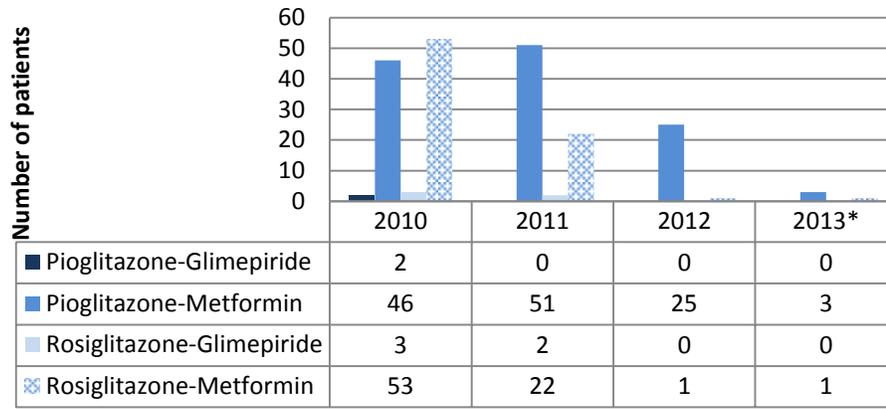
Number of patients on single-ingredient TZDs



Number of claims for combination TZD products



Number of patients on combination TZDs



* 2013 UTILIZATION DATA IS FOR PART OF 2013 AND MAY NOT BE COMPLETE DUE TO SIGNIFICANT DELAYS IN THE PROCESSING OF ACO CLAIMS INFORMATION

Conclusions

The most important factors to consider are safety and efficacy of the different treatment options. Other priorities when selecting type 2 diabetes medications include minimizing the risk of hypoglycemia and weight gain as these too are matters that affect safety, adherence, and cost.²⁵ Various patient and medication factors should be considered on an individual patient basis in order to select the most appropriate treatment option(s).^{25,27}

According to the ADA Standards of Medical Care in Diabetes 2013³⁵, current clinical guidelines^{25,27,36} and recent systematic reviews and meta-analyses of randomised controlled trials⁶⁵, metformin remains the cornerstone of type 2 anti-diabetic treatment. Advantages of metformin include low risk of hypoglycemia, can promote modest weight loss, and it has a robust cardiovascular safety profile.²⁵ If metformin alone is inadequate, the guidelines include various options as add-on therapy with a focus on individualized goals of treatment. Special populations such as patients with chronic kidney disease may require dose reductions or medications could be contraindicated in which case alternative treatments should be considered.

Pioglitazone has relatively potent A1C-lowering properties and a low risk of hypoglycemia, but is associated with side-effects which are limiting its use including weight gain and fluid retention, an elevated risk for chronic edema or heart failure, increased bone fracture risk, and a potential increased risk of bladder cancer.^{25,27} The implication of the restricted access program for rosiglitazone is that patients who were taking rosiglitazone and benefiting from the drug were able to continue if they chose to do so. However, rosiglitazone will only be available to new patients if they are unable to achieve glucose control on other medications and are unable to take pioglitazone, the only other thiazolidinedione.^{5,8}

The FDA and the European Medicines Agency issued warnings and updated the pioglitazone label to warn against starting pioglitazone in patients with active bladder cancer and to use caution if starting pioglitazone in patients with a prior history of bladder cancer. Although evidence is limited, results from a meta-analysis⁷ and a nested case control study⁶⁴ suggest that the risks for pioglitazone (bladder cancer risk) may outweigh the benefits.

The number of patients on TZDs (in the Utah Medicaid population) appears to be decreasing, but approximately 300-500 patients are taking pioglitazone-containing products. Efforts to ensure metformin has been tried or excluded as a first-line option (e.g. contraindications) would benefit patients. Overall, the TZDs have a limited role due primarily to safety concerns.

Appendix 1 –Drug Comparison – Additional Information

	Pioglitazone (Actos) ^{29,30}	Rosiglitazone (Avandia) ^{29,59}
Class	Antidiabetic; thiazolidinedione	Antidiabetic; thiazolidinedione
Contraindications	Heart failure, New York Heart Association Class III or IV Hypersensitivity to pioglitazone hydrochloride or any other component of the product	Heart failure, NYHA class III and IV
Warnings and Precautions	<p>Congestive heart failure: Fluid retention may occur and can exacerbate or lead to congestive heart failure. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk. Monitor patients for signs and symptoms.</p> <p>Edema: Dose-related edema may occur.</p> <p>Hepatic effects: Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ACTOS and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ACTOS if liver injury is confirmed and no alternate etiology can be found.</p> <p>Fractures: Increased incidence in female patients. Apply current standards of care for assessing and maintaining bone health.</p> <p>Bladder cancer: Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer.</p> <p>Hypoglycemia: When used with insulin or an insulin secretagogue, a lower dose of the insulin or insulin secretagogue may be needed to reduce the risk of hypoglycemia.</p> <p>Macular edema: Postmarketing reports. Recommend regular eye exams in all patients with diabetes according to current standards of care with prompt evaluation for acute visual changes.</p> <p>Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOS or any other anti-diabetic drug.</p>	<p>Fluid retention, which may exacerbate or lead to heart failure, may occur. Combination use with insulin and use in congestive heart failure NYHA Class I and II may increase risk of other cardiovascular effects.</p> <p>Increased risk of myocardial infarction has been observed in a meta-analysis of 52 clinical trials (incidence rate 0.4% versus 0.3%).</p> <p>Coadministration of AVANDIA and insulin is not recommended.</p> <p>Dose-related, weight gain, and anemia may occur.</p> <p>Macular edema has been reported.</p> <p>Increased incidence of bone fracture.</p>
Pregnancy Category	C	C
Breast Feeding	Micromedex: Infant risk cannot be ruled out	Micromedex: Infant risk cannot be ruled out

	Pioglitazone (Actos) ^{29,30}	Rosiglitazone (Avandia) ^{29,59}
Major Drug Interactions	Dabrafenib (theoretical) Ifosfamide (theoretical) Tolvaptan (theoretical)	Abiraterone Acetate (theoretical) Dabrafenib (theoretical)
Adverse Reactions	<p>Most common adverse reactions (≥ 5% and at a rate higher than with placebo) include upper respiratory tract infection, headache, sinusitis, myalgia, and pharyngitis.</p> <p><i>Micromedex (Pioglitazone):</i> <u>Common</u> Cardiovascular: Edema (4.8% to 15.3%) Endocrine metabolic: Weight increased Hematologic: Anemia (less than or equal to 2%) Musculoskeletal: Fracture of bone (5.1%), Myalgia (5.4%) Neurologic: Headache (9.1%) Respiratory: Pharyngitis (5.1%), Sinusitis (6.3%), Upper respiratory infection (13.2%) <u>Serious</u> Cardiovascular: Congestive heart failure Hepatic: ALT/SGPT level raised (0.3%), Liver failure Ophthalmic: Diabetic macular edema Renal: Malignant tumor of urinary bladder (0.16% to 0.44%) Respiratory: Pneumonia</p>	<p>Common adverse reactions (>5%) reported in clinical trials without regard to causality were upper respiratory tract infection, injury, and headache.</p> <p><i>Micromedex (Rosiglitazone):</i> <u>Common</u> Cardiovascular: Edema (4.8% to 25%) Endocrine metabolic: Weight gain <u>Serious</u> Cardiovascular: Angina, Congestive heart failure, Myocardial infarction, Myocardial ischemia Hepatic: Cholestatic hepatitis, Hepatotoxicity (0.2% to 0.32%) Neurologic: Cerebrovascular accident Ophthalmic: Diabetic macular edema (Very rare) Respiratory: Pleural effusion, Pneumonia, Pulmonary edema</p>
Potential for weight gain (Adverse effect)	Weight Gain: Dose-related weight gain occurs when ACTOS is used alone or in combination with other anti-diabetic medications. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.	<p>Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure [see Boxed Warning].</p> <p>In a 4- to 6-year, monotherapy, comparative trial (ADOPT) in patients recently diagnosed with type 2 diabetes not previously treated with antidiabetic medication, the median weight change (25th, 75th percentiles) from baseline at 4 years was 3.5 kg (0.0, 8.1) for AVANDIA, 2.0 kg (-1.0, 4.8) for glyburide, and -2.4 kg (-5.4, 0.5) for metformin. In a 24-week trial in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.</p>

	Pioglitazone (Actos) ^{29,30}	Rosiglitazone (Avandia) ^{29,59}
Monitoring	<ul style="list-style-type: none"> ○ Improvements in fasting blood glucose and HbA1c levels are indicative of efficacy ○ HbA1c, at least twice yearly in patients who are meeting treatment goals; every 3 months, for patients whose therapy has changed and/or who are not meeting glycemic goals ○ Self-monitoring of blood glucose (SMBG) to assist in meeting needs and goals of therapy ○ Liver function tests; prior to initiating therapy and promptly in any patient who reports symptoms of liver injury (fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice) ○ Signs and symptoms of congestive heart failure and fluid retention (excessive or rapid weight gain, dyspnea, or edema); following initiation and after any dose increase ○ Bone health; particularly in female patients, according to current standards of care during treatment 	<ul style="list-style-type: none"> ○ Improvements in fasting blood glucose and HbA1c levels are indicative of efficacy ○ HbA1c, at least twice yearly in patients who are meeting treatment goals; every 3 months, for patients whose therapy has changed and/or who are not meeting glycemic goals ○ Self-monitoring of blood glucose (SMBG) to assist in meeting needs and goals of therapy ○ Liver enzymes, baseline and periodically thereafter ○ Signs and symptoms of heart failure following therapy initiation and after any dose increase
Alcohol (Micromedex Clinical Teaching section)	No information found in product label	<p>Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption.</p> <p>Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.</p>

Note: Clinical trials are conducted under widely varying conditions and for varying durations, so adverse reaction frequencies observed in the clinical trials of one drug cannot be directly compared with frequencies in the clinical trials of another drug and may not reflect the frequencies observed in practice.

References

1. Insulin. <http://en.wikipedia.org/wiki/Insulin>. Accessed 14 August 2013.
2. Diabetes Drugs: Sulfonylureas. <http://www.diabetesselfmanagement.com/Blog/Mark-Marino/diabetes-drugs-sulfonylureas/>. Accessed 14 August 2013.
3. Bennett WL, Balfe LM, Faysal JM. AHRQ's comparative effectiveness research on oral medications for type 2 diabetes: a summary of the key findings. *J Manag Care Pharm*. Jan-Feb 2012;18(1 Suppl A):1-22.
4. Doctors Concerned as India Suspends Diabetes Drug Pioglitazone. <http://www.medscape.com/viewarticle/807446>. Accessed 14 August 2013.
5. Pediatric Type 2 Diabetes Mellitus Medication. <http://reference.medscape.com/article/925700-medication>. Accessed 14 August 2013.
6. Troglitazone.
7. Kermod-Scott B. Meta-analysis confirms raised risk of bladder cancer from pioglitazone. *Bmj*. 2012;345:e4541.
8. Q&A: Avandia (rosiglitazone). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226976.htm>. Accessed 14 August 2013.
9. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021071&Product_No=002&table1=OB_Rx. Accessed 15 August 2013.
10. *Costco Pharmacy Pricing Information*.
11. Pioglitazone (Lexi-Drugs). http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7497#f_pharmacology-and-pharmacokinetics. Accessed 15 August 2013.
12. Drugs at FDA: FDA Approved Drug Products. . <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed 15 August 2013.
13. Diabetes treatment: Medications for type 2 diabetes. <http://www.mayoclinic.com/health/diabetes-treatment/DA00089>.
14. Insulin therapy in type 2 diabetes mellitus. http://www.uptodate.com/contents/insulin-therapy-in-type-2-diabetes-mellitus?source=see_link. Accessed 29 October 2012.
15. Amylin. Bydureon (exenatide extended-release) injectable suspension [package insert]. San Diego, CA: Amylin Pharmaceuticals, Inc; 2012.
16. NovoNordisk. Victoza (liraglutide - rDNA origin) injection solution [package insert]. Plainsboro, NJ: Novo Nordisk A/S; 2013.
17. Amylin. Byetta (exenatide) injection solution [package insert]. San Diego, CA: Amylin Pharmaceuticals, Inc; 2011.
18. Lexi-Comp I, ed *Drug Information Handbook*. 21st ed. Hudson, OH: Lexi-Comp; 2013.
19. AHFS Drug Information, ed *AHFS 2013 Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
20. Powers AC. Chapter 344. Diabetes Mellitus. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.
21. Powers AC, D'Alessio D. Chapter 43. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2011.
22. INVOKANA (canagliflozin) tablets product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf. Accessed 15 August 2013.
23. Bromocriptine (Lexi-Drugs) http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6475. Accessed 20 August 2013.

24. CYCLOSET® (bromocriptine mesylate) Tablets Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020866s002lbl.pdf. Accessed 20 August 2013.
25. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement - executive summary. *Endocr Pract.* May-Jun 2013;19(3):536-557.
26. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* Jan 2009;32(1):193-203.
27. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* Jun 2012;35(6):1364-1379.
28. Pharmacist's Letter/Prescriber's Letter. Drugs for Type 2 Diabetes. June 2012: 280601. <http://prescribersletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=&s=PRL&pt=2&segment=4408&dd=280601>. Accessed 22 August 2013.
29. Micromedex Drug Comparison - Pioglitazone and Rosiglitazone. <http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugCompareResults>. Accessed 22 July 2013.
30. ACTOS (pioglitazone hydrochloride) tablets product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf. Accessed 22 July 2013.
31. Rosiglitazone Maleate (AHFS Essentials (Adult and Pediatric)). http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/410725. Accessed 19 August 2013.
32. Rosiglitazone Maleate [Your search: rosiglitazone]. <http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch>. Accessed 19 August 2013.
33. AACE Comprehensive Diabetes Management Algorithm. <https://www.aace.com/publications/algorithm>. Accessed 20 August 2013.
34. Sherwin R, Jastreboff AM. Year in diabetes 2012: the diabetes tsunami. *J Clin Endocrinol Metab.* Dec 2012;97(12):4293-4301.
35. Executive summary: standards of medical care in diabetes--2013. *Diabetes Care.* Jan 2013;36 Suppl 1:S4-S10.
36. Global Guideline for Type 2 Diabetes. 2012; <http://www.idf.org/global-guideline-type-2-diabetes-2012>.
37. Type 2 diabetes: final scope. <http://www.nice.org.uk/nicemedia/live/13675/61437/61437.pdf>. Accessed 22 August 2013.
38. CG87 Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide. <http://guidance.nice.org.uk/CG87/QuickRefGuide/pdf/English>. Accessed 22 August 2013.
39. Dietary Supplement Fact Sheet: Vitamin B12. <http://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/>. Accessed 21 August 2013.
40. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians (ACP). https://www.acponline.org/mobile/clinicalguidelines/guidelines/oral_treatment_type2_diabetes_0212.html. Accessed 22 August 2013.
41. McCulloch D. Management of persistent hyperglycemia in type 2 diabetes mellitus. <http://www.uptodate.com/contents/management-of-persistent-hyperglycemia-in-type-2-diabetes-mellitus?view=print>.

42. McCulloch D. Initial management of blood glucose in type 2 diabetes mellitus. http://www.uptodate.com/contents/initial-management-of-blood-glucose-in-type-2-diabetes-mellitus?source=see_link&anchor=H13#H13.
43. Standards of medical care in diabetes--2013. *Diabetes Care*. Jan 2013;36 Suppl 1:S11-66.
44. Repaglinide (Lexi-Drugs). http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7617#f_dosages. Accessed 21 August 2013.
45. Nateglinide (Lexi-Drugs). http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7348#f_dosages. Accessed 21 August 2013.
46. Rosak C, Mertens G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes Metab Syndr Obes*. 2012;5:357-367.
47. Pramlintide (Lexi-Drugs). http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7538. Accessed 26 August 2013.
48. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. Nov 2012;60(5):850-886.
49. Bailey CJ, Turner RC. Metformin. *N Engl J Med*. Feb 29 1996;334(9):574-579.
50. DeFronzo RA. Bromocriptine: a sympatholytic, d2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care*. Apr 2011;34(4):789-794.
51. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab*. May 2010;12(5):384-392.
52. Ahren B. Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin--diabetes control and potential adverse events. *Best Pract Res Clin Endocrinol Metab*. Aug 2009;23(4):487-498.
53. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab*. Jan 2011;13(1):7-18.
54. Deacon CF, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes-a review and meta analysis. *Diabetes Obes Metab*. Aug 2012;14(8):762-767.
55. INSULIN. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/065D9C/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/787039/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=0002&contentSetId=31&title=INSULIN&servicesTitle=INSULIN. Accessed 26 August 2013.
56. 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*. Oct 8 2005;366(9493):1279-1289.
57. Rosiglitazone (Lexi-Drugs). http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7641#f_dosages. Accessed 26 August 2013.
58. Management of hyperglycemia in patients with type 2 diabetes and pre-dialysis chronic kidney disease or end-stage renal disease. http://www.uptodate.com/contents/management-of-hyperglycemia-in-patients-with-type-2-diabetes-and-pre-dialysis-chronic-kidney-disease-or-end-stage-renal-disease?topicKey=NEPH%2F1857&elapsedTimeMs=0&source=search_result&searchTerm=type+2+diabetes&selectedTitle=48~150&view=print&displayedView=full#. Accessed 26 August 2013.
59. Avandia (rosiglitazone) product label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021071s041lbl.pdf. Accessed 20 August 2013.

60. FDA Drug Safety Communication: Updated drug labels for pioglitazone-containing medicines. <http://www.fda.gov/Drugs/DrugSafety/ucm266555.htm>. Accessed 14 August 2013.
61. 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*. Apr 2011;34(4):916-922.
62. FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. <http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm>. Accessed 14 August 2013.
63. Update on ongoing European review of pioglitazone-containing medicines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001275.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1. Accessed 14 August 2013.
64. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *Bmj*. 2012;344:e3645.
65. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *Bmj*. 2012;344:e1369.