Hypoglycemics, Thiazolidinediones (TZDs)

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
TZDs		
pioglitazone (Actos®)[1]	generic	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
rosiglitazone (Avandia®)[2]	GlaxoSmithKline	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
TZDs and glimepiride		
pioglitazone/ glimepiride (Duetact™)[3]	generic	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and sulfonylurea combination or who are not adequately controlled on either agent alone
rosiglitazone/ glimepiride (Avandaryl®)[4]	GlaxoSmithKline	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with dual rosiglitazone and glimepiride therapy is appropriate
TZDs and metformin		
pioglitazone/ metformin (Actoplus Met®)[5]	generic	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and metformin combination or who are not adequately controlled on either agent alone
pioglitazone/ metformin extended-release (Actoplus Met XR®)[6]	Takeda	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and metformin combination or who are not adequately controlled on either agent alone
rosiglitazone/ metformin (Avandamet®)[7]	GlaxoSmithKline	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

A fixed-combination of pioglitazone and DPP-4 inhibitor, pioglitazone/alogliptin (Oseni®), is approved as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both pioglitazone and alogliptin is appropriate. Oseni will not be reviewed here.

OVERVIEW

It is estimated that 29.1 million Americans have diabetes.[8] Increasing rates of obesity support the projection that cases of diabetes will continue to grow. Diabetes causes a significant economic burden, both in terms of direct and indirect costs, to society. It is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic complications, including blindness and renal dysfunction.[9]

Three metabolic defects are responsible for the progression to type 2 diabetes mellitus: peripheral insulin resistance, impaired β-cell function, and increased hepatic glucose production.[10] The thiazolidinediones (TZDs) work by decreasing insulin resistance. Combination products of TZDs with metformin, alogliptin, and glimepiride are available and may improve adherence for those patients requiring combination therapy.

In 2015, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes were updated and included the sodium-glucose cotransporter-2 (SGLT2) inhibitors to the management algorithm for

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type 2 diabetes.[11] The position statement recommends HbA1c of less than 7 percent, as a reasonable target for most nonpregnant patients. Metformin is recommended for the treatment of type 2 diabetes, along with lifestyle interventions at the time of diagnosis, unless metformin is contraindicated.[12] If metformin fails to produce the target HbA1c after three months of therapy, either a TZD, sulfonylurea, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist, or insulin should be added. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, insulin therapy should be considered, with or without additional agents. If target HbA1c is still not achieved after an additional three months, then an agent from a different group listed should be added. Therapy should be individualized based on the needs, preferences, and tolerances of each patient. Patients with type 2 diabetes are at increased risk of cardiovascular morbidity and mortality; therefore, aggressive management of cardiovascular risk factors (e.g., blood pressure and lipid therapy, antiplatelet treatment, and smoking cessation) should be part of multifactorial risk reduction approach.[13]

The 2013 Consensus Panel of the American Association of Clinical Endocrinologists (AACE) issued a comprehensive algorithm for glycemic control in patients with type 2 diabetes.[14] In order to minimize the risk of diabetes related complications, the algorithm specifies a goal of HbA1c of 6.5 percent or less for healthy patients with a low risk of hypoglycemia and an individualized goal higher than 6.5 for patients with concurrent illness and a high risk of hypoglycemia. Patients are stratified based on their current HbA1c levels to monotherapy, dual therapy, and triple therapy, including seven major classes of oral medications (biguanides, dipeptidyl-peptidase-4 [DPP-4] inhibitors, thiazolidinediones, alpha glucosidase inhibitors [AGIs], sulfonylureas, meglitinides, and bile acid sequestrants) and insulin therapy (basal, premixed, and multiple daily injections). The choices of medications are prioritized according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost. For the patient with an HbA1c level less than 7.5 percent, it is possible that a single agent might achieve the HbA1c goal of 6.5 percent. Because of its safety and efficacy, metformin is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy, unless contraindicated. Alternative monotherapy agents include a GLP-1 receptor agonist, DPP-4 inhibitor, or AGI which offer fewer adverse events or possible greater benefits compared to TZDs, sulfonylureas, and sodium-dependent cotransporter 2 (SGLT2) inhibitors which should be used with caution. For the patient with an HbA1c level within the range of 7.5 percent to 9.0 percent, dual therapy may be necessary. As a result of its safety and efficacy, metformin should be the cornerstone of dual therapy for most patients. When dual therapy is insufficient, then triple therapy or insulin may be needed. GLP-1 receptor agonists and DPP-4 inhibitors are also recommended before the use of TZDs, which should still be used with caution in dual and triple therapy. These guidelines state glucose targets should be individualized and take into account residual life expectancy, duration of disease, cardiovascular disease risk factors, and comorbid conditions; the patient's psychological, social, and economic status should also be considered.

TZDs have been reported to increase high-density lipoprotein cholesterol (HDL-C), and reduce triglycerides levels (pioglitazone only), blood pressure, inflammatory markers, hepatic steatosis, and carotid and coronary artery thickening. TZDs may also help prevent central nervous system insulin resistance-related cognitive dysfunction.[15]

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PHARMACOLOGY

TZDs bind and activate peroxisome proliferator-activated receptor gamma (PPAR-γ) in skeletal muscle, adipose tissue, and the liver, resulting in improved insulin action by enhancing the sensitivity of peripheral muscle glucose uptake and possibly reducing hepatic glucose production.[16,17] The TZDs require the presence of insulin to exert its antihyperglycemic effect.

Metformin (Glucophage®), a biguanide, decreases hepatic glucose production decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[18,19,20]

Glimepiride (Amaryl®) is a member of the sulfonylureas, which enhance response of pancreatic beta cells to glucose, in turn stimulating the release of insulin.[21,22]

TZDs and sulfonylureas primarily affect fasting blood glucose. Metformin affects both fasting and postprandial blood glucose levels. The reduction of HbA1c due to any of these agents is expected to be approximately 1 percent to 1.5 percent. The duration of glycemic control with TZDs appears to be maintained over periods up to five to six years. Glucose lowering is maximal at six months with sulfonylureas, and glucose levels return towards baseline at about three years. Metformin appears intermediate in duration in its glucose lowering effects.[23,24]

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
glimepiride (Amaryl)[25,26]	100	5–9.2	Two inactive metabolites	renal: 60 feces: 40
metformin (Glucophage)[27]	50-60	6.2	None	renal: >90
pioglitazone (Actos)[28]	--	3–7 (parent); 16–24 (parent plus metabolites)	M-II, M-III, M-IV (active in animal models)	renal: 15–30 (as metabolites) feces: majority of dose
rosiglitazone (Avandia)[29]	99	3–4	Yes, inactive	renal: 64 feces: 23

In bioequivalence studies of all combination products, both the TZD and the metformin or glimepiride component were bioequivalent to the single agents administered together.[30, 31, 32, 33, 34]

CONTRAINDICATIONS/WARNINGS [35,36,37,38,39,40,41]

TZD-containing products carry boxed warnings regarding the development or exacerbation of congestive heart failure in some patients. After initiation of TZD therapy, and after dose increases, patients should be observed carefully for signs and symptoms of heart failure including excessive, rapid weight gain, dyspnea, and/or edema. If these signs and symptoms develop, heart failure should be managed according to the current standards of care. Discontinuation or dose reduction of TZD must be considered. The initiation of TZD therapy in patients with NYHA Class III or IV heart failure is contraindicated.

In 2011, due to elevated risk of cardiovascular events as reported in cardiovascular safety data, including data from the long-term clinical study, Rosiglitazone Evaluated for Cardiac Outcomes and

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Regulation of Glycemia in Diabetes (RECORD), use of rosiglitazone and rosiglitazone-containing medicines had been significantly restricted.[42] However, in November 2013, after further review of the evaluation of the RECORD trial, the FDA found that evidence of increased risk of heart attack or death in patients treated with rosiglitazone were lacking and removed the prescribing and distribution restrictions.[43,44] Rosiglitazone use is no longer limited to certain patients, distribution is no longer limited to certain pharmacies, and enrollment in the REMS program is no longer required. The FDA has also removed the requirement for a clinical trial comparing rosiglitazone to pioglitazone and standard diabetes drugs.

In 2010, the FDA issued a safety announcement regarding a possible association of pioglitazone (Actos) use for more than one year with an increased risk of bladder cancer.[45] Results from an observational study suggest that the risk increases with duration of use. Consequently, use of pioglitazone is not recommended in patients with active bladder cancer and should be used with caution in those with a prior history of bladder cancer, considering the benefits of glycemic control versus unknown risks for cancer recurrence.[46]

Labeling for rosiglitazone/glimepiride (Avandaryl) and pioglitazone/glimepiride (Duetact) contains a warning for increased risk of cardiovascular mortality due to the sulfonylurea component. In addition, the glimepiride component may cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. A non-sulfonylurea should be considered as an alternative in these patients.

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal dysfunction (serum creatinine greater than 1.5 mg/dL for males and greater than 1.4 mg/dL for females), acute or chronic metabolic acidosis, including diabetic ketoacidosis (with or without coma), and pregnancy. Lactic acidosis is a rare, but potentially fatal, complication of metformin therapy. The risk is greater for patients experiencing sepsis, dehydration, hypoxemia, hypoperfusion, hepatic and renal impairment, or those who consume excess alcohol. Metformin should be used with caution in patients undergoing radiologic procedures who need intravenous iodinated contrast agents.

Use of glimepiride, metformin, pioglitazone, or rosiglitazone is contraindicated in patients with known hypersensitivity to these products or any of their components.

For all products containing pioglitazone or rosiglitazone, liver function tests are recommended at the start of therapy, then periodically thereafter at the discretion of the physician. Increased in alanine aminotransferase (ALT) levels should be monitored closely; and if ALT exceeds 2.5 to 3 times the upper limit of normal (ULN), the drug should be discontinued.

Dose-related weight gain has been observed in patients taking pioglitazone and rosiglitazone either alone or in combination with other hypoglycemic agents.

TZDs should be used with caution in patients with edema. Edema was reported more frequently in patients treated with pioglitazone or rosiglitazone than placebo; effects appear to be dose related.

Dose-related fluid retention may occur particularly when TZDs are used in combination with insulin, and may lead to or exacerbate heart failure.[47] Patients treated with insulin and a PPAR-γ agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be treated appropriately, and dose reduction or discontinuation of the PPAR-γ agonist must be considered.

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Dose-related decreases in mean hemoglobin and hematocrit may occur in adults taking pioglitazone or rosiglitazone, either alone or in combination with other hypoglycemic agents.

In premenopausal anovulatory women, the initiation of therapy with pioglitazone or rosiglitazone may cause ovulation; therefore, patients may be at an increased risk for pregnancy. Adequate contraception is recommended.

Do not use pioglitazone or rosiglitazone to treat type 1 diabetes or diabetic ketoacidosis.

In PROactive, a randomized trial with type 2 diabetes patients, an increased incidence of bone fractures was noted in pioglitazone use (5.1 percent versus 2.5 percent for placebo).[48] This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures were nonvertebral (lower and upper limb), and no increase was seen in men taking pioglitazone.

Based on a review of the safety data from the ADOPT study, rosiglitazone labeling includes mention of an increased number of arm, hand, and foot fractures among women taking rosiglitazone for newly diagnosed type 2 diabetes.[49] The fracture rate was 2.74 per 100 patient years for the 645 women treated with rosiglitazone versus 1.54 per 100 patient-years for the 590 women in the metformin arm and 1.29 per 100 patient-years for 605 women treated with glyburide. The increase in fractures was in the humerus, hand, and foot for women taking rosiglitazone; there was no increase in hip or spine fractures, usually associated with postmenopausal osteoporosis.

Macular edema has been reported in post-marketing experience in diabetic patients on TZD therapy. Some patients had improvement in their macular edema after discontinuation of TZD therapy. It is not known if not there is a causal relationship between TZDs and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist and should be promptly referred to an ophthalmologist if any type of visual symptom is reported.

Risk Evaluation and Mitigation Strategy (REMS)[50,51,52,53,54,55,56]

In November 2013, the FDA lifted its restriction on rosiglitazone-containing products. These agents are once again available through retail and mail-order pharmacies and health care professionals, pharmacies, and patients are no longer be required to enroll in the rosiglitazone REMS program. However, manufacturers are required to provide education on the cardiovascular risk of rosiglitazone to health care professionals who are likely to prescribe rosiglitazone. A Medication Guide continues to be included as a part of the approved labeling for rosiglitazone-containing products, to inform patients about the serious risks associated with its use.

The REMS requirement for pioglitazone-containing products was eliminated; however, the Medication Guide is maintained as part of the approved labeling.

DRUG INTERACTIONS[57, 58, 59, 60, 61, 62, 63]

Pioglitazone and rosiglitazone are predominantly metabolized by CYP2C8. If an inhibitor or inducer of CYP2C8 is started or stopped during treatment with either agent, changes in treatment may be needed based on clinical response. Additionally, to a much lesser extent, rosiglitazone is also metabolized by CYP2C9, and pioglitazone is metabolized by CYP3A4.

Exercise caution when using TZDs with drugs that are known to exacerbate hyperglycemia.

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Although, no dosing changes are recommended, there is a potential for drug interactions with TZDs and cationic drugs (e.g., such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine; however, no specific dosing changes are recommended.

ADVERSE EFFECTS

Drug	Headache	Edema	Myalgia/ Fatigue	Anemia	Hyperglycemia	Diarrhea	Hypoglycemia
glimepiride (Amaryl)[64] n=746	1.5	nr	nr	nr	nr	<1	0.9–1.7
metformin (Glucophage)[65] n=141	5.7 (4.8)	nr	1-5	nr	nr	53.2 (11.7)	1–5
pioglitazone (Actos)[66]	9.1 (6.9)	4.8 (1.2)	5.4 (2.7)	≤2	5.1 (8.1)	nr	reported
rosiglitazone (Avandia)[67] n=2,526	5.9 (5)	4.8 (1.3)	3.6 (5)	1.9 (0.7)	3.9 (5.7)	2.3 (3.3)	0.6 (0.2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive. Incidences in parentheses are placebo. nr = not reported.

Adverse effects reported in the labeling for Actoplus Met, Actoplus Met XR, Avandaryl, Avandamet, and Duetact do not reflect the specific combination product.

Edema and CHF

In clinical studies, the incidence of edema with the combination of pioglitazone and insulin was 15.3 percent and with insulin and placebo was seven percent. In a 16-week study, 1.1 percent of patients receiving insulin and pioglitazone developed heart failure, compared to no patients on insulin therapy alone.[68]

In a 26-week study, the incidence of edema with rosiglitazone in combination with insulin was 14.7 percent, whereas insulin alone was 5.4 percent.[69] New onset of heart failure was one percent with insulin, two percent with rosiglitazone 4 mg with insulin, and three percent with rosiglitazone 8 mg with insulin.

Combined and peripheral edema was reported more frequently in patients taking combination pioglitazone/metformin therapy (six percent) than metformin/placebo (2.5 percent).[70, 71] Edema was also higher in patients receiving rosiglitazone/metformin therapy (4.4 percent) than metformin/placebo (2.2 percent).

Hypoglycemia

Hypoglycemia was reported more frequently in patients taking combination rosiglitazone/metformin therapy (three percent) than rosiglitazone (0.6 percent) or metformin (1.3 percent) monotherapy.[72]

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Anemia

Anemia was also reported in a greater number of patients taking combination rosiglitazone/metformin therapy (7.1 percent) compared to rosiglitazone (1.9 percent) or metformin (2.2 percent) monotherapy. Anemia was reported in less than two percent of patients taking pioglitazone/metformin therapy.[73,74]

Effect on Cholesterol/Triglycerides

Drug	Total-Cholesterol	HDL Cholesterol	LDL Cholesterol	Triglycerides
pioglitazone (Actos)[75] versus placebo	↑ 3.3-6.4%* ↑ 4.4%	↑ 12.2-19.1% ↑ 8.1%	↑ 5.2-7.2%* ↑ 4.8%	↓ 9.0-9.6% ↑ 4.8%
rosiglitazone (Avandia)[76] versus placebo	↑ (percent increase not reported)	↑ 11.4-14.2% ↑ 8%	↑ 14.1-18.6% ↑ 4.8%	variable

*not significantly different from placebo

SPECIAL POPULATIONS[77,78,79,80,81,82,83]

Pediatrics

The safety and effectiveness have not been established for pioglitazone (Actos) or rosiglitazone (Avandia) or their combination products in pediatric patients.

Pregnancy

All pioglitazone- and rosiglitazone- containing products are Pregnancy Category C.

According to ADA 2015 Standard of Medical Care guidelines, HbA1c goal of 7 percent or less is appropriate in pregnant women, only if it can be safely achieved.[84]

Abnormal blood glucose levels during pregnancy are associated with increased neonatal morbidity and mortality, and a higher incidence of congenital anomalies. The use of insulin during pregnancy is most often recommended to manage blood glucose levels in pregnant patients with diabetes.

Ethnic groups

A randomized, double-blind, placebo-controlled, parallel-group study was performed to determine the efficacy and tolerability of the addition of rosiglitazone to a regimen of glyburide once daily in African-American and Hispanic-American patients with type 2 diabetes inadequately controlled with sulfonylurea monotherapy.[85] Patients were assigned to receive treatment with glyburide 10 or 20 mg daily plus rosiglitazone 8 mg or placebo daily for 24 weeks. The primary efficacy endpoint was the change from baseline in HbA1c after 24 weeks of treatment. A total of 245 patients (101 African-Americans, 144 Hispanic-Americans) were enrolled. In the overall study population, a significantly greater mean reduction from baseline in HbA1c was seen with glyburide/rosiglitazone compared with glyburide/placebo (between-group difference: -1.4 percent; $p<0.001$). When assessed by ethnicity, HbA1c values were significantly reduced with glyburide/rosiglitazone compared with glyburide/placebo in African-American patients and in Hispanic-American patients (both $p<0.001$). With glyburide/rosiglitazone, 17.6 percent of African-American patients and 25.8 percent of Hispanic-

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American patients achieved HbA1c less than 7 percent, compared with 4.5 and 1.4 percent of glyburide/placebo patients, respectively. The most frequently reported adverse events with glyburide/rosiglitazone were edema and weight increase.

DOSAGES[86,87,88,89,90,91,92,93,94]

Drug	Initial dose	Maintenance dose	Availability
TZDs			
pioglitazone (Actos)	15–30 mg daily	15–45 mg daily	15, 30, 45 mg tablets
rosiglitazone (Avandia)	4 mg daily OR 2 mg twice daily	2–4 mg twice daily OR 8 mg daily	2, 4, 8 mg tablets
TZDs and glimepiride			
pioglitazone/glimepiride (Duetact)	Prior therapy with glimepiride or pioglitazone: 30 mg/2 mg or 30 mg/4 mg once daily with the first meal of the day Maximum daily dose: 45 mg/8 mg		30 mg/2 mg, 30 mg/4 mg tablets
rosiglitazone/glimepiride (Avandaryl)	4 mg/1 mg once daily with the first meal of the day (consider 4 mg/2 mg if patient was on prior TZD or sulfonylurea therapy) Maximum daily dose: 8 mg/4 mg		4 mg/1 mg, 4 mg/2 mg, 4 mg/4 mg, 8 mg/2 mg, 8 mg/4 mg tablets
TZDs and metformin			
pioglitazone/metformin (Actoplus Met)	15 mg/500 mg or 15 mg/850 mg tablets once or twice daily with food Max daily dose: 45 mg/2,550 mg administered in divided doses with food		15 mg/500 mg, 15 mg/850 mg tablets
pioglitazone/metformin extended-release (Actoplus Met XR)	15 mg/1000 mg or 30 mg/1000 mg tablets once daily with evening meal Max daily dose: 45 mg/2000 mg administered once daily with evening meal		15 mg/1000 mg, 30 mg/1000 mg tablets
rosiglitazone/metformin (Avandamet)	No prior therapy with metformin and/or rosiglitazone 2 mg/500 mg once or twice daily. If HbA1c >11% or FPG >270 mg/dL, consider a starting dose of 2 mg/500 mg twice daily		2 mg/500 mg, 4 mg/500 mg, 2 mg/1,000 mg, 4 mg/1,000 mg tablets
	Prior therapy with metformin 1,000 mg/day: 2 mg/500 mg twice daily Prior therapy with metformin 2,000 mg/day: 2 mg/1,000 mg twice daily		
	Prior therapy with rosiglitazone 4 mg/day: 2 mg/500 mg twice daily Prior therapy with rosiglitazone 8 mg/day: 4 mg/500 mg twice daily		

Pioglitazone and rosiglitazone may be taken without regard to meals. No dosage adjustment is required in patients with renal impairment.

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CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. In countries outside of the U.S., blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

Very few comparative clinical trials of the combination products are available at this time. There is one trial comparing a fixed-dose combination product to its component ingredients.

pioglitazone (Actos) and placebo

A total of 408 patients with type 2 diabetes were randomized in a multicenter, double-blind, placebo-controlled trial.[95] Patients had HbA1c greater than 7 percent and fasting plasma glucose (FPG) >140 mg/dL, and were randomized to receive placebo or pioglitazone 7.5, 15, 30, or 45 mg daily for 26 weeks. Patients treated with 15, 30, or 45 mg pioglitazone had significant mean decreases in HbA1c (-1.0 to -1.6 percent difference from placebo) and FPG (-39.1 to -65.3 mg/dL difference from placebo). The decreases in FPG were observed as early as the second week of therapy; maximal decreases occurred after 10 to 14 weeks and were maintained until the end of therapy. The subset of patients naïve to therapy had greater improvements in HbA1c and FPG (difference from placebo of -2.55 percent and -79.9 mg/dL for the 45 mg group, respectively) compared with previously treated patients. The overall adverse event profile of pioglitazone was similar to that of placebo, with no evidence of hepatotoxicity or ALT elevations.

Patients (n=197) with type 2 diabetes, HbA1c greater than 8 percent, and FPG greater than 7.7 mmol/L were enrolled in a 23-week, double-blind trial and randomized to receive either placebo or pioglitazone 30 mg daily.[96] Efficacy parameters included HbA1c and FPG. Compared with placebo, pioglitazone significantly (p=0.0001) reduced HbA1c (-1.37 percent) and FPG (-3.19 mmol/L). The overall adverse event profile of pioglitazone was similar to that of placebo, with no evidence of drug-induced elevations of ALT concentrations or hepatotoxicity.

A double-blind, randomized, placebo-controlled study involved daily administration of pioglitazone 15 or 30 mg or placebo daily in patients with type 2 diabetes (n=251) for 26 weeks.[97] HbA1c was reduced by -0.92 and -1.05 percent in the pioglitazone groups, respectively, and FBG was reduced by -34.3 and

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-36.0 mg/dL, respectively, compared with placebo. Both doses of pioglitazone significantly reduced postprandial blood glucose levels at all visits (-163 and -165 mg/dL/hour, respectively) compared with an increase of 47.7 mg/dL/hour on placebo. The type and frequency of adverse events were similar in all treatment groups.

pioglitazone (Actos) and insulin

In a 16-week, double-blind, multicenter study, 566 patients currently on a stable insulin regimen for at least 30 days who continued to have an HbA1c greater than 8 percent were randomized to receive daily placebo or pioglitazone 15 mg or 30 mg.[98] At the end of treatment, patients receiving pioglitazone 15 mg or 30 mg had mean decreases in HbA1c (-1 and -1.3 percent, respectively; p<0.0001) and FPG (-34.5 and -48 mg/dL, respectively; p<0.0001) that were significantly lower than baseline and the placebo group. The 15 mg and 30 mg pioglitazone groups had significant increases in HDL-C, while the 30 mg group showed significant mean reductions in triglyceride levels compared to placebo. The incidences of weight increase, hypoglycemia, and edema were higher among patients receiving insulin plus pioglitazone.

pioglitazone (Actos), metformin (Glucophage), and insulin

In a multicenter, double-blind study, 222 patients with HbA1c >8 percent at screening were given titrated insulin therapy and then were randomly assigned to 20-week treatment with pioglitazone or placebo in combination with insulin, with or without concurrent metformin therapy.[99] More than 98 percent of patients were taking metformin prior to and during the study. Pioglitazone significantly reduced insulin dose requirements two weeks after treatment initiation (p<0.05). At the end of the study, pioglitazone reduced daily insulin dosages by 12 units (p<0.001). Relative to placebo, pioglitazone reduced daily insulin dosages by 12.7 units, while improving mean HbA1c levels (pioglitazone -1.6 versus placebo -1.4 percent; p=NS). More pioglitazone-treated patients experienced edema and weight gain than placebo-treated patients.

pioglitazone/metformin (Actoplus Met) versus pioglitazone (Actos) versus metformin (Glucophage)

In a double-blind, randomized, parallel-group, controlled, 24-week study, 600 patients with type 2 diabetes were randomized to receive pioglitazone 15 mg/metformin 850 mg twice daily, pioglitazone 15 mg twice daily, or metformin 850 mg twice daily.[100] The primary endpoint was change from baseline in HbA1c of pioglitazone/metformin combination therapy compared with pioglitazone and metformin monotherapy. Secondary endpoints included change from baseline in FPG, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). Safety and tolerability of pioglitazone/metformin combination therapy and its individual components were also evaluated. Patients with HbA1c greater than 8.6 percent at baseline showed the greatest decrease in HbA1c with the fixed-dose combination product (-1.83 percent; p<0.0001) versus with monotherapy pioglitazone (-0.96 percent) and with monotherapy metformin (-0.99 percent). In addition, 63.8 percent of patients using the fixed-dose combination achieved HbA1c of 7 percent or less versus 46.9 percent and 38.9 percent of patients receiving pioglitazone and metformin monotherapy, respectively. The decrease from baseline FPG was significantly larger in the pioglitazone/metformin fixed-dose combination group (-39.9 mg/dL) (p<0.01) compared with either monotherapy. Also, the decrease in mean HOMA-IR was greatest with the combination therapy group. Overall, treatment with combination therapy

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demonstrated greater efficacy than its individual components. The fixed-dose combination was well tolerated, with reduced or similar adverse event rates compared with each individual monotherapy. This study was funded by the manufacturer of the fixed dose combination product.

pioglitazone (Actos), rosiglitazone (Avandia), and glimepiride (Amaryl)

A 12-month, multicenter, double-blind, randomized, controlled, parallel-group trial assessed 91 patients with type 2 diabetes and metabolic syndrome.[101] All patients had poor glycemic control or experienced one or more adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin. All patients received a fixed oral dose of glimepiride 4 mg/day for 12 months. Patients also were randomized to receive pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily for 12 months. Patients in both groups experienced significant increases in mean BMI at 12 months compared with baseline (4.92 and 6.17 percent, respectively; $p<0.05$). At 12 months, a 1.3 percent reduction in mean values for HbA1c ($p<0.01$), 19.3 percent in FPG ($p<0.01$), and 16.3 percent in postprandial plasma glucose ($p<0.01$) were observed; no significant differences were found between treatment groups. Although the glimepiride/pioglitazone group experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline, the glimepiride/rosiglitazone group experienced a significant increase in most lipid-related risk factors for cardiovascular disease. Of the 87 patients who completed the study, 6.7 percent of patients in the glimepiride/pioglitazone group and 11.9 percent of patients in the glimepiride/rosiglitazone group had transient, mild to moderate adverse events that did not cause withdrawal from the trial.

pioglitazone (Actos), rosiglitazone (Avandia), glimepiride (Amaryl), and metformin (Glucophage)

A randomized, double-blind, placebo-controlled, parallel-group, two-arm study enrolled 170 patients with type 2 diabetes.[102] Patients received glimepiride 2 mg (titrated to effect) or placebo in combination with an established regimen of immediate- or extended-release metformin and rosiglitazone or pioglitazone for 26 weeks. The primary efficacy outcome was the change in HbA1c from baseline. HbA1c was significantly improved at endpoint with glimepiride combination therapy compared with placebo (-1.31 versus -0.33 percent, respectively; $p<0.001$). Of the patients who received glimepiride, 62.2 percent achieved an HbA1c value of less than 7 percent, compared with 26 percent of patients receiving placebo ($p<0.001$). At endpoint, the glimepiride combination significantly lowered FPG (-37.4 mg/dL; $p<0.001$), as well. Clinically significant adverse events, laboratory abnormalities, and rates of severe hypoglycemia were similar between treatment groups. The overall incidence of hypoglycemia, however, was 51.2 percent in the glimepiride group and 8.3 percent in the placebo group ($p<0.001$).

rosiglitazone (Avandia) and placebo

Three hundred and sixty-nine patients with type 2 diabetes were enrolled in a double-blind, parallel-group, placebo-controlled study.[103] Patients were randomly assigned to receive placebo or rosiglitazone at doses of 4, 8, or 12 mg daily. At eight weeks, FPG decreased significantly in the rosiglitazone 4 mg, 8 mg, and 12 mg groups (-0.9, -2.0, and -1.7 mmol/L; $p=0.0003$, $p<0.0001$, and $p<0.0001$, respectively) compared with placebo (+0.4 mmol/L). Improvements in FPG were seen for rosiglitazone 4 and 8 mg groups, but the 12 mg/day dose produced no additional improvement. The overall incidence of adverse events was similar in all treatment groups.

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In a double-blind study, 959 patients were randomized to placebo or rosiglitazone 4 mg or 8 mg for 26 weeks. The primary measure of efficacy was change in the HbA1c concentration.[104] Rosiglitazone produced reductions in HbA1c of -0.8 to -1.5 percent compared with placebo. Approximately 33 percent of drug-naïve patients treated with rosiglitazone achieved HbA1c less than 7 percent at study end. The proportions of patients with at least one adverse event were comparable among the rosiglitazone and placebo groups, with no evidence of hepatotoxicity in any treatment group.

After a four-week placebo run-in period, 493 patients with type 2 diabetes were randomized in a double-blind manner to receive rosiglitazone 2 mg or 4 mg or placebo twice daily for 26 weeks.[105] The primary endpoint was change in HbA1c. Rosiglitazone 2 and 4 mg twice daily decreased mean HbA1c relative to placebo by -1.2 and -1.5 percentage points, respectively, and reduced FPG concentrations relative to placebo by -3.22 and -4.22 mmol/L, respectively. There was no increase in adverse events with rosiglitazone.

After a two-week placebo run-in phase, 303 patients with type 2 diabetes were randomly assigned in double-blind fashion to eight weeks of treatment with placebo or 2, 4, or 6 mg of rosiglitazone twice daily (FDA-approved maximum dose is 8 mg daily).[106] All rosiglitazone doses significantly reduced FPG compared with baseline and showed significantly reduced peak postprandial glucose concentrations compared with baseline ($p<0.001$) and with placebo ($p<0.0001$). Rosiglitazone 4 and 6 mg twice daily regimens prevented increases in HbA1c that were observed in the placebo group. The proportion of patients with one or more adverse event was similar in all four treatment groups with no evidence of hepatotoxicity.

rosiglitazone (Avandia), glyburide (Micronase®, DiaBeta®), and metformin (Glucophage)

The efficacy and safety of adding rosiglitazone to an established regimen of glyburide/metformin in patients with type 2 diabetes who had not achieved adequate glycemic control (HbA1c between seven and 10 percent) were evaluated.[107] Following an open-label, lead-in phase, 365 patients randomly received rosiglitazone 4 mg once daily or placebo in a double-blind manner. Based on glycemic response, rosiglitazone dose was maintained or increased to 4 mg twice daily. After 24 weeks, therapy with glyburide/metformin plus rosiglitazone resulted in a greater reduction (-1 percent, $p<0.001$) in HbA1c levels compared with combination therapy that included placebo (+0.1 percent). A larger proportion of patients (42 versus 14 percent) in the triple combination group attained HbA1c levels less than 7 percent. The difference in FBG levels between groups was -48 mg/dL ($p<0.001$), favoring glyburide/metformin plus rosiglitazone. Adverse events of rosiglitazone reflected those reported in similar studies.

rosiglitazone (Avandia) and glipizide (Glucotrol)

A total of 227 patients with type 2 diabetes who were being treated with submaximal doses of sulfonylureas were randomized to receive rosiglitazone 4 mg or placebo daily in combination with glipizide 10 mg twice daily for two years in a double-blind, parallel-group study.[108] Rosiglitazone/glipizide significantly decreased HbA1c, FPG, insulin resistance, plasma free fatty acids, and medical care utilization and improved treatment satisfaction compared with glipizide alone.

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rosiglitazone (Avandia) and insulin

Three hundred nineteen patients with type 2 diabetes with mean baseline HbA1c greater than 7.5 percent and taking insulin twice daily were randomized in a double-blind manner to 26 weeks of additional treatment with rosiglitazone 4 or 8 mg daily or placebo.[109] Insulin dose could be decreased for safety reasons. The primary endpoint was reduction of HbA1c from baseline. By intent-to-treat analysis, treatment with rosiglitazone plus insulin resulted in a mean reduction from baseline in HbA1c of -1.2 percent ($p<0.0001$), with a 12 percent mean reduction of insulin dosage. Serious adverse events did not differ among groups.

rosiglitazone (Avandia) and metformin (Glucophage)

The efficacy of the combination of metformin and rosiglitazone compared to metformin alone was evaluated in 348 patients with type 2 diabetes who were inadequately controlled on metformin alone.[110] Patients were randomized in a double-blind fashion to metformin 2,500 mg daily plus placebo, metformin 2,500 mg plus rosiglitazone 4 mg daily, or metformin 2,500 mg daily plus rosiglitazone 8 mg daily for 26 weeks. HbA1c, FPG, insulin sensitivity, and β-cell function improved significantly with the combination therapy in a dose-dependent manner. The mean HbA1c decrease was one percent in the rosiglitazone 4 mg group and 1.2 percent in the rosiglitazone 8 mg group. Twenty-eight percent of patients in the rosiglitazone 8 mg group achieved HbA1c less than seven percent. Dose-dependent increases in body weight and lipid profiles were observed. Adverse effects were similar in all groups.

The efficacy and safety of rosiglitazone 2 mg or 4 mg twice daily, in combination with metformin 2,500 mg daily, were evaluated in 116 patients whose type 2 diabetes was inadequately controlled with metformin alone.[111] The randomized, double-blind, placebo-controlled study was conducted for 26 weeks. Mean HbA1c levels decreased significantly from baseline to week 26 in the rosiglitazone 2 mg (-0.7 percent; $p=0.0052$) and 4 mg (-1.2 percent; $p=0.0008$) groups, but increased in the placebo group (+0.3 percent; $p=0.2651$). Mean FBG levels also improved significantly with metformin plus rosiglitazone therapy in a dose-dependent manner compared with placebo ($p<0.0019$). The proportion of patients with one or more adverse events was similar across all three groups, with no cases of hepatotoxicity.

In a double-blind, randomized, parallel-group study, 766 subjects with a baseline metformin dose of 1,000 mg/day were randomized to receive either rosiglitazone 4 mg daily (4 mg/1,000 mg) or an additional 500 mg/day of metformin.[112] Increases in the study medications to maximum doses were performed after eight weeks. After 24 weeks, rosiglitazone 8 mg/metformin 1,000 mg was at least as effective as 2,000 mg/day of metformin in improving HbA1c with mean reductions of -0.93 and -0.71 percent, respectively, from baseline in subjects that completed the study. In addition, a higher percentage of subjects in the rosiglitazone/metformin group achieved HbA1c less than 7 percent (58.1 versus 48.4 percent). The percentage of subjects experiencing a gastrointestinal side effect was 27.9 and 38.7 percent for the rosiglitazone/metformin and metformin groups, respectively.

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META-ANALYSES

pioglitazone (Actos)

To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events, a database containing individual patient-level, time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.[113] The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. Data from a total of 19 trials, enrolling 16,390 patients, were combined by means of a fixed-effects model. Study drug treatment duration ranged from four months to 3.5 years. The primary outcome occurred in 375 of 8,554 patients (4.4 percent) receiving pioglitazone and 450 of 7,836 patients (5.7 percent) receiving control therapy (hazard ratio [HR], 0.82; 95% CI, 0.72-0.94; p=0.005). Individual components of the primary endpoint were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3 percent) of the pioglitazone (Actos)-treated patients and 139 (1.8 percent) of the control patients (HR, 1.41; 95% CI, 1.14-1.76; p=0.002). Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

pioglitazone (Actos) and rosiglitazone (Avandia)

A systematic review and meta-analysis of seven randomized, double-blind clinical trials of drug-related congestive heart failure in patients given TZDs (either rosiglitazone or pioglitazone) was performed.[114] The main outcome measures were development of congestive heart failure and the risk of cardiovascular death. Of the 20,191 patients, 360 who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). Results showed no heterogeneity of effects across studies, which indicated a class effect for TZDs. Compared with controls, patients given TZDs had increased risk for development of congestive heart failure across a wide background of cardiac risk (relative risk 1.72; p=0.002). By contrast, the risk of cardiovascular death was not increased with either of the two TZDs (0.93; p=0.68).

rosiglitazone (Avandia)

Published literature, the FDA website, and a clinical trials registry maintained by the drug manufacturer were searched for studies with the following criteria: study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes.[115] The inclusion criteria were met by 42 studies. All occurrences of myocardial infarction and death from cardiovascular causes were tabulated. Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline HbA1c was approximately 8.2 percent. Compared to the control group, the odds ratio for the rosiglitazone group for myocardial infarction was 1.43 (95% CI, 1.03 to 1.98; p=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; p=0.06).

TZDs and bone loss

A meta-analysis was conducted in patients with type 2 diabetes to confirm the effects of TZDs on bone are a drug class effect.[116] PPAR-γ activation with TZDs leads to unbalanced bone remodeling: bone

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resorption increases and bone formation decreases. Risk factors for development of TZD-induced secondary osteoporosis are gender (women), age (elderly), and duration of treatment.

SUMMARY

As seen in the clinical trials, pioglitazone (Actos) and rosiglitazone (Avandia) are capable of lowering HbA1c by one to one and one-half percentage points when used as monotherapy in the treatment of type 2 diabetes. In combination with other agents used to lower blood glucose levels, including metformin and glimepiride, the level of HbA1c lowering is approximately an additional one-half to one percent.

In measuring the ability of pioglitazone and rosiglitazone to reduce other markers, such as fasting plasma glucose, reductions of 40 to 60 mg/dL are possible with monotherapy, according to clinical trials. In combination with other antidiabetic agents, additional decreases of 25 to 50 mg/dL are seen.

In 2011, due to elevated risk of cardiovascular events, use of rosiglitazone and rosiglitazone-containing medicines had been significantly restricted; however, in November 2013, after further review of the data, the FDA found that evidence of increased risk of heart attack or death in patients treated with rosiglitazone were lacking and removed the prescribing and distribution restrictions. According to FDA communications, the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer.

The addition of combination products with metformin or glimepiride will allow administration that is more convenient for patients who require multiple drugs, but with added precautions for their use. Comparative data with these agents are limited and only include ingredient comparisons to the fixed-dose combination products or their components.

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