

drug information perspectives

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PIOGLITAZONE

TRADE NAME: ACTOS

CLASSIFICATION: Thiazolidinedione; antidiabetic; insulin sensitizer; "glitazone"

ACTION: Selective agonist for PPAR-gamma (peroxisome proliferator-activated receptor-gamma), a transcription factor. Decreases insulin resistance in adipose tissue, skeletal muscle and liver cells through activation of PPAR-gamma, which alters transcription of several insulin-responsive genes involved in the regulation of glucose and lipid metabolism. Reduces free fatty acid release (free fatty acid is a mediator of insulin resistance in obesity). Results include enhanced insulin-dependent glucose uptake, reduced hepatic gluconeogenesis, and reduced hyperglycemia and hyperinsulinemia with no increase in endogenous insulin secretion. Effective only in the presence of insulin. Induces favorable changes in cardiovascular risk factors (increased HDL cholesterol, decreased triglycerides, decreased density and increased size of LDL particles, decreased carotid intima-media thickness, decreased C-reactive protein). May also activate PPAR-alpha. Decreases intrahepatic fat.

PHARMACOKINETICS

- **Half-life:** 3-7 hours (pioglitazone); 26-28 hours (major active metabolites).
- **Absorption:** Well absorbed; absolute bioavailability approximately 80%. Peak plasma concentration reached within 2 hours (fasting state). Food delays time to peak concentration to 3-4 hours but does not reduce absorption.
- **Distribution:** Protein binding >99%.
- **Metabolism:** Undergoes extensive hepatic metabolism, mainly via CYP 2C8 and secondarily by CYP 3A4, 2C9 and extrahepatic 1A1/2. There are three active metabolites.
- **Elimination:** Mainly eliminated in feces; 15-30% as metabolites in urine.
- **Special populations:**
 - **Renal impairment:** Half-life unchanged in moderate to severe renal impairment; maximum concentration and AUC decreased in severe renal impairment.
 - **Hepatic impairment:** Mean peak plasma concentrations (pioglitazone plus active metabolites) reduced by 45% but AUC unchanged (see PRECAUTIONS).
 - **Elderly:** AUC slightly increased, and half-life slightly prolonged; changes not considered clinically important.
 - **Females:** Cmax and AUC increase 20-60%.

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USES AND EFFICACY

Type 2 diabetes mellitus: As monotherapy or in combination with other antidiabetic agents, produces dose-related improvement in glycemic control (HbA1c decreases from baseline by 0.3-0.9% with monotherapy and by 0.6-1.8% with combination therapy). Fasting plasma insulin levels also decrease. Improves the classic dyslipidemia of diabetes, high triglycerides and low HDL, by reducing triglycerides up to 16% and increasing HDL up to 20%.

Major clinical trials

Monotherapy (2000): In a double-blind, placebo-controlled dose-ranging trial, 408 type 2 diabetic patients were randomized to receive placebo or 7.5, 15, 30, or 45 mg of pioglitazone once daily for 26 weeks (*Diabetes Care* 2000;23:1605-11). Pioglitazone 15, 30, and 45 mg groups showed a significant decrease in HbA1c at week 26 (decrease from baseline by 0.3%, 0.3%, and 0.9%, respectively). All 4 dose groups had a significant decrease in fasting plasma glucose from baseline (decrease by 1.00, 1.64, 1.77, and 3.01 mmol/L, respectively). There was a significant decrease from baseline in fasting plasma insulin at 30 and 45 mg doses and in serum triglycerides at 15, 30, and 45 mg doses (9-9.6% decrease), and significant dose-related increases in HDL cholesterol at all dose levels (8-19% increase). Study limitations: 69% of patients had taken other antihyperglycemic drugs prior to the study, and discontinuation of that therapy may have altered their initial response.

Combination with sulfonylurea (2001): In a double-blind, placebo-controlled trial, 560 inadequately controlled type 2 diabetic patients were randomized to receive either placebo or pioglitazone 15 mg or 30 mg once daily in addition to their current sulfonylurea regimens for 16 weeks (*Am J Med* 2001;111:10-17). At study end, pioglitazone 15 mg and 30 mg groups had a significant decrease vs both baseline and placebo in HbA1c (0.8% and 1.2% vs baseline) and fasting plasma glucose (1.88 and 2.90 mmol/L vs baseline). The 30 mg group had a significant decrease from baseline in fasting plasma insulin.

Combination with metformin (2000): In a double-blind, placebo-controlled trial, 328 inadequately controlled type 2 diabetic patients were randomized to receive either placebo or pioglitazone 30 mg once daily in addition to their current metformin regimens (*Clin Ther* 2000;22:1395-1409). At week 16, the pioglitazone + metformin group had a significant decrease in HbA1c (0.6% from baseline) and fasting plasma glucose (2.09 mmol/L), compared with the placebo + metformin group. The pioglitazone + metformin group showed a decrease from baseline in fasting insulin (14.6 pmol/L) and triglycerides (9.7%) and an increase from baseline in HDL-cholesterol (10%) (all changes statistically significant). Study limitation: 30% of patients had discontinued antihyperglycemic drugs which could have altered their initial response.

Combination with insulin (2002): In a double-blind, placebo-controlled trial, 566 inadequately controlled type 2 diabetic patients were randomized to receive placebo or pioglitazone 15 or 30 mg once daily in addition to their current insulin regimens (*Int J Clin Pract* 2002;56:251-7). By week 16, pioglitazone 15 mg and 30 mg groups showed a significant decrease vs both baseline and placebo in HbA1c (1.0 and 1.3% vs baseline, respectively) and fasting plasma glucose (1.92 and 2.67 mmol/L vs baseline, respectively). Pioglitazone increased HDL-cholesterol 9%; increased LDL cholesterol (6.5% with 15 mg) and decreased triglycerides (24%) with 30 mg doses of pioglitazone. Hypoglycemia was more common in patients taking insulin plus pioglitazone, occurring in 15% of those patients vs 5% taking insulin alone. Weight gain was a concern (mean 2.3-3.7kg).

PROactive Study (PROspective pioglitAZone Clinical Trial In macroVascular Events, 2005): In a randomized, double-blind trial, 5238 patients with type 2 diabetes (baseline HbA1c 7.0-8.9) and evidence of macrovascular complications were given placebo or pioglitazone in adjusted doses, as well as continued and optimized therapy with concurrent sulfonylureas, metformin, insulin, or lipid-altering, antihypertensive, and antiplatelet drugs (*Lancet* 2005;366(9493):1279-89). After a mean of 34.5 months, HbA1c decreased by 0.5%, triglycerides decreased by about 10%, HDL increased by 9%, and blood pressure decreased by a median 3mm Hg. The primary outcome measure (composite of all-cause mortality, nonfatal MI, stroke, major leg amputation, acute coronary syndrome, CABG, PCI, or leg revascularization) occurred in 58 fewer patients given pioglitazone, but this difference was not statistically significant. A secondary outcome measure (composite of all-cause mortality, nonfatal MI and stroke) occurred in 57 fewer patients given pioglitazone (absolute risk reduction 2%, relative risk reduction 16%, p=0.027). There were significantly more events of heart failure (417 vs 302 with placebo), and heart failure requiring hospitalization, in patients given pioglitazone. The investigators concluded that pioglitazone reduces the composite of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events. Study limitations: The primary endpoint did not reach statistical significance, and the secondary endpoint is therefore not statistically significant when adjusted for multiple testing. The reduction in

blood pressure could explain any cardiovascular benefit. Finally, results were not consistent with benefit, since the rate of leg revascularization was numerically higher and serious heart failure was more common in the pioglitazone group.

Clinical course

After initiating treatment, HbA1c decrease is evident within 4-14 weeks and maximal within 18 to 22 weeks (in some studies 36 weeks). A decrease in fasting plasma glucose is evident within 2 weeks, and maximal after 6 to 14 weeks. Weight gain usually begins in the first few weeks and then plateaus.

Place in therapy

As an adjunct to diet and exercise, pioglitazone is effective in type 2 diabetes as monotherapy or combination therapy, with a change in HbA1c in the range of other oral antihyperglycemic drugs. For some patients, the associated weight gain may be unacceptable. In newly diagnosed patients with inadequate response to diet alone, pioglitazone is as effective as a sulfonylurea or metformin for glycemic control. Sulfonylureas are more quickly effective but the benefit is not as sustained as with pioglitazone. In patients inadequately controlled by a sulfonylurea, adding pioglitazone improves glycemic control and achieves comparable benefit to adding metformin, with better effect on triglycerides and HDL, but more edema and weight gain. Similarly, pioglitazone is beneficial in patients with an inadequate response to metformin. In patients inadequately controlled with insulin therapy, add-on pioglitazone improves HbA1c, although weight gain, edema and hypoglycemia are more likely, and this drug combination is not approved in Canada. Compared with rosiglitazone, efficacy is comparable in diabetes but only pioglitazone lowers triglyceride levels. Although the PROactive study (2005) concluded that pioglitazone reduces cardiovascular events by 16%, there are questions about the interpretation of this study (see Major Clinical Trials). In the UKPDS study, metformin reduced total mortality by 36% and microvascular and macrovascular diabetic complications by 32%, a superior result. Pioglitazone may be most useful in (1) patients who cannot take metformin or sulfonylureas, (2) patients who have secondary failure on metformin or sulfonylureas, (3) patients with renal impairment, and (4) patients with a low risk of heart failure.

Advantages

- Once daily dosing without regard to meals.
- Low risk of hypoglycemia if given alone.
- Safe in patients with renal insufficiency (unlike metformin).
- Lowers serum triglycerides and increases HDL-cholesterol with no effect on LDL (advantage over sulfonylureas, rosiglitazone, and better than metformin).
- Efficacy maintained over one year of treatment.

Disadvantages

- Contraindicated in patients with serious hepatic insufficiency, or NYHA Class II, III or IV heart failure.
- Causes fluid retention and peripheral edema (may exacerbate or precipitate heart failure). Long-term cardiovascular safety unknown.
- Can cause weight gain (metformin, in contrast, reduces weight). Although this does not appear to involve an increase in abdominal adipose tissue which is associated with cardiovascular disease, the health implications are unknown and this could result in an increase in noncompliance.
- A benefit in reducing diabetic microvascular and macrovascular diabetic complications is unproven (unlike metformin, sulfonylureas).
- Nonresponse rate for this type of drug is approximately 25%, mainly in patients with low insulin secretion.
- Long-term response rate uncertain with progressive beta-cell failure, since insulin is required for activity; in some studies HbA1c trends upwards with time.

Investigational/unapproved uses

Plaque psoriasis: Sixty percent of patients showed significant improvement in one trial.

Polycystic ovary syndrome: Improves insulin sensitivity and hyperandrogenism, and induces ovulation and regular menstrual cycles in 40%. Similar efficacy to metformin but increases body weight.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity** to pioglitazone or any tablet component.
- **Serious hepatic impairment.**

- Acute **heart failure** and NYHA class II, III or IV heart failure (risk of exacerbation).
- **Pregnancy and lactation**.
- **Type 1 diabetes and diabetic ketoacidosis** (ineffective, requires insulin to work).

Precautions

- **Monitor liver function:** Severe, rarely fatal liver toxicity has occurred with another thiazolidinedione (troglitazone). Do not initiate therapy in patients who have developed liver disease while taking troglitazone, have evidence of active liver disease or have increased baseline serum transaminase levels (ALT > 2.5 times upper limit of normal). In all patients, monitor liver function tests before and after initiation of therapy, every 2 months for the first year, and periodically thereafter. Alternatively, some authorities recommend monitoring in the first year only as clinically indicated. Caution in patients with mild liver dysfunction (ALT 1 to 2.5 times upper limit of normal) at baseline or during therapy; increase frequency of monitoring. Discontinue therapy if persistent increases in ALT to >3 times upper limit of normal, or if jaundice develops.
- **Edema or heart failure:** Fluid retention and plasma volume expansion may occur, exacerbating or precipitating heart failure. Discontinue treatment if clinical heart failure occurs. Caution in patients with underlying risk factors for congestive heart failure, including prior edema, myocardial infarction or symptomatic coronary artery disease, hypertension, left ventricular hypertrophy, significant aortic or mitral valve heart disease, current treatment with drugs associated with fluid retention, chronic renal failure, or advanced age. Monitor all patients, regardless of cardiac status, for signs and symptoms of congestive heart failure, including excessive weight gain, pedal edema, and dyspnea.
- **Polycystic ovary syndrome, anovulatory premenopausal women with insulin resistance:** Resumption of ovulation may occur; effective contraception recommended.
- **Weight gain:** Caution if unusually rapid weight gain occurs; assess for fluid retention, edema, and congestive heart failure.
- **Combination with insulin** (increased risk of hypoglycemia, edema, heart failure, weight gain).
- **Combination therapy with oral hypoglycemic agents** (hypoglycemia may occur; consider reducing dose of concomitant agent).
- **Report** any unexpected or serious reactions to Health Canada's adverse reaction monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789).

PREGNANCY AND LACTATION

Not recommended during pregnancy; no human data. Embryotoxicity in animals observed at doses in excess of maximum recommended human doses. Insulin is the drug of choice for management of diabetes during pregnancy.

Secreted into milk of lactating rats; expected to be secreted into human breast milk. No human data. Use during breast-feeding should be avoided.

SIDE EFFECTS

Frequency of occurrence (greater than rate seen with placebo) given in brackets (for monotherapy, except where indicated).

Cardiovascular: Edema (with increased plasma volume; up to 18%; monotherapy: 3.6%; combination with sulfonylurea: 5%; combination with metformin: 2.9%; combination with insulin: 8%; dose-related); heart failure (cases); pulmonary edema (cases).

CNS: Headache (4%).

Endocrine/Metabolic: Mild to moderate hypoglycemia (rare with monotherapy since it does not induce insulin release; combination with sulfonylurea 3.2%; during combination with insulin 3-10%; dose-related).

Hematologic: Decreased hemoglobin values by 2-4%, decreased hematocrit and erythrocyte count (usually not clinically significant).

Hepatic: Hepatitis, elevated ALT, mixed hepatocellular-cholestatic liver injury; fatal and nonfatal liver failure (rare case reports).

Respiratory: Upper respiratory tract infection (4.7%); pharyngitis (4.3%); sinusitis (1.7%).

Other: Weight gain (dose-related, variable, may be continuous; due largely to increased subcutaneous fat but no increase in visceral fat, and perhaps fluid retention; usually no increase in appetite; median of 4.5 kg after 48 weeks of monotherapy, and 5.4 kg after 60 weeks or more of combination therapy with sulfonylurea or metformin; may be more than 10kg in rare cases). Elevated serum creatine phosphokinase level to >10 times upper limit of normal (case reports). Bladder cancer (cases, causality unclear). Arthralgia (8%). Lack of efficacy. Myalgia (2.7%). Fractures (mainly in distal upper and lower limbs; increased risk in women compared with other oral diabetes medication; excess risk of 0.8 fractures per 100 patient-years of use).

INTERACTIONS

DRUG	EFFECT	MECHANISM	IMPORTANCE
Atorvastatin	Elevated atorvastatin and pioglitazone levels	Unknown	Caution, monitor serum glucose and lipid levels
Gemfibrozil	Elevated pioglitazone level	Decreased metabolism (via CYP2C8)	Caution; monitor blood glucose; use reduced dose
Hypoglycemics, oral	Hypoglycemia	Unknown	Adjunctive; caution, reduce dose of hypoglycemic
Insulin	Increased risk of edema, weight gain, heart failure, hypoglycemia	Additive or synergistic	Caution; monitor
Ketoconazole	Elevated pioglitazone level	Decreased metabolism	Caution; monitor blood glucose
Midazolam	Decreased midazolam level	Increased metabolism (3A4 induction)	Caution; monitor effect
Nifedipine	Increased nifedipine level	Unknown	Caution
Oral contraceptive	Decreased ethinyl estradiol level	Unknown	Caution
Rifampin	Potential decreased pioglitazone	Increased metabolism	Caution; monitor blood glucose

Pioglitazone is a weak inducer of CYP 3A4. Lack of pharmacokinetic interaction has been shown with: itraconazole, simvastatin. It does not alter the pharmacokinetics of warfarin or digoxin.

DOSAGE

Adults:

Type 2 diabetes:

Oral: Monotherapy or in combination with sulfonylurea, metformin, or insulin: Initially, 15 mg or 30 mg once daily without regard to meals. If response is inadequate, dose may be increased in increments up to a maximum of 45 mg once daily. Use lowest effective dose. Adequate trial: at least 3 months, possibly as long as 36 weeks for full effect on HbA1c.

For patients receiving a sulfonylurea: If hypoglycemia occurs, reduce dose of sulfonylurea.

For patients receiving insulin: If hypoglycemia occurs or if plasma glucose concentration decreases to less than 5.5 mmol/L (100 mg/dL), decrease insulin dose by 10% to 25%. Make further dose adjustments based on glucose-lowering response.

Elderly: No dosage adjustment required.

Renal impairment: No dosage adjustment required.

Hepatic impairment: Do not initiate therapy if patient exhibits evidence of active liver disease or has increased baseline serum transaminase levels (ALT >2.5 times upper limit of normal). In patients with mild hepatic enzyme elevations but no evidence of active liver disease: no dosage adjustment required, but use with caution and with frequent monitoring of liver function (see PRECAUTIONS). Discontinue pioglitazone if ALT increases to 3 times upper limit of normal and remains elevated, or if jaundice develops.

Congestive heart failure (NYHA Class I) or presence of 1 or more risk factors for congestive heart failure:

Initially, 15 mg once daily without regard to meals. Increase dosage gradually only after several months of treatment, as required to achieve glycemic control, with close monitoring for excessive weight gain, peripheral edema, or signs of exacerbation/development of congestive heart failure (see PRECAUTIONS).

Females: Cmax and AUC increased 20-60% and effect on HbA1c greater; no routine dosage adjustment recommended but dosage should be individualized.

NURSING IMPLICATIONS

Pioglitazone is given once daily with or without food.

Pioglitazone can cause fluid retention and edema, which can exacerbate or lead to heart failure. Observe patients for signs and symptoms of heart failure, including excessive weight gain, pedal edema, and dyspnea.

Hypoglycemia rarely occurs with pioglitazone therapy alone. The risk is increased when used in combination with other antidiabetic agents. Observe patients for drug-induced hypoglycemia (weakness, sweating, tachycardia, confusion).

Rarely, hepatotoxicity has been reported. Observe the patient for signs of hepatotoxicity (unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, jaundice). Discontinue the medication and notify the physician immediately.

Ensure that patients are on a diabetic diet.

PATIENT INSTRUCTIONS

Pioglitazone (pye-oh-GLI-ta-zone) is used to treat type 2 diabetes (formerly referred to as non-insulin-dependent diabetes) as an addition to diet and regular exercise. It may be used alone or in combination with another antidiabetic drug. It helps your body use its own insulin more efficiently, so that glucose (sugar) is metabolized more easily.

While taking this and other antidiabetic drugs, it is important to have your blood glucose and glycosylated hemoglobin tested regularly, as instructed, to monitor how well the medication is working.

Take this medication as prescribed by your physician. It may be taken with meals or on an empty stomach. It should be taken at the same time each day, at a time that is the easiest for you to remember.

If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose, and take your dose at the regular time on the following day. Do not take a double dose to make up for the missed dose.

It usually takes a few months before the full effects of the medication occur.

This medication is generally well tolerated. Some patients develop headaches. Other side effects include weight gain and swelling in the ankles or feet.

Call your physician immediately if you develop shortness of breath, weakness, fatigue, swollen ankles, or unusual weight gain. These symptoms may indicate an effect on the heart.

Very rarely, this medication has been reported to affect the liver. If you experience nausea, vomiting, stomach pain, lack of appetite, dark urine, or yellowing of the skin or whites of your eyes, discontinue this medication and call your physician immediately. Because of this rare side effect, your physician will likely order a blood test to check your liver function before you start taking this medication, and periodically while you are taking it.

In premenopausal women with certain medical conditions associated with ovulatory disorders, such as polycystic ovary syndrome, this medication can cause the return of ovulation. Therefore, in order to prevent pregnancy, it may be necessary to institute or modify contraceptive measures. Discuss such measures with your physician.

Pioglitazone may alter the effectiveness of oral contraceptives and cause breakthrough bleeding. Discuss with your physician the possible need to adjust the dose of oral contraceptive or use alternative methods of contraception while using pioglitazone.

Maintain close contact with your physician while taking this medication.

If you have experienced any unexpected or serious reactions to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number. Also ensure that your physicians are informed of any adverse effects and record this for the future.

Store this medication in a labelled container, in a dry, cool place, out of the reach of children.

PRESENTATION:

Tablets: 15, 30, 45 mg.

References are available on request.