PIOGLITAZONE (Systemic)

Category

Antidiabetic agent.

Indications

Accepted

Diabetes, type 2 (treatment)¾Pioglitazone is indicated as adjunctive therapy to diet and exercise in the management of patients with type 2 diabetes mellitus (previously referred to as non-insulin-dependent diabetes mellitus [NIDDM]). Pioglitazone may be used as monotherapy 1, 2, 3 or in combination with a sulfonylurea, metformin, or insulin 1, 3.

Pharmacology

Mechanism of action/Effect:

Pioglitazone is a thiazolidinedione antidiabetic agent that is effective only in the presence of insulin. Its primary action is to decrease insulin resistance at peripheral sites and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. These effects are accomplished through selective binding at the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), which is found in adipose tissue, skeletal muscle, and the liver. Activation of these receptors modulates transcription of several insulin-responsive genes that control glucose and lipid metabolism. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue 1.

Precautions to Consider

Carcinogenicity

During a 2-year carcinogenicity study conducted in male and female rats, no drug-induced tumors were observed except for benign and/or malignant transitional cell neoplasms of the urinary bladder. These were observed only in male rats at doses of 4 mg per kg of body weight (mg/kg) per day and above (approximately equal to the maximum recommended human oral dose based on mg per square meter of body surface area [mg/m]). Oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m) were used in this study. Drug-induced tumors were not observed in any organ in male and female mice given oral doses up to 100 mg/kg per day (approximately 11 times the maximum recommended human oral dose based on mg/m) 1.

During clinical trials, no new cases of bladder tumors were detected in more than 1800 patients treated with pioglitazone. Abnormal urinary cytology was observed in 0.72% and 0.88% of patients treated with pioglitazone and placebo, respectively 1.

Mutagenicity

No evidence of mutagenicity was found in the Ames bacterial assay, a mammalian cell forward gene mutation assay, an in vitro cytogenetics assay, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay 1.

Pregnancy/Reproduction

Fertility¾Pioglitazone therapy may cause resumption of ovulation in premenopausal anovulatory patients with insulin resistance 1.

No evidence of impaired fertility was found in male and female rats given pioglitazone in oral dose of 40 mg/kg per day (approximately 9 times the maximum recommended human oral dose based on mg/m2) throughout mating and gestation. 1

Pregnancy¾Studies have not been done in humans 1.

It is recommended that insulin alone be used during pregnancy for maintenance of blood glucose concentrations that are as close to normal as possible. Abnormal maternal blood glucose concentrations have been associated with a higher incidence of congenital anomalies and increased neonatal morbidity and mortality 1.

Teratogenicity was not observed in rats treated with oral pioglitazone at doses of up to 80 mg/kg or in rabbits treated with up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m, respectively). In rats treated with oral pioglitazone at doses of 10 mg/kg and above (approximately 2 times the maximum recommended human oral dose based on mg/m) during late gestation and lactation, delayed postnatal development was observed 1.

FDA Pregnancy Category C. 1

Breast-feeding

It is not known whether pioglitazone is distributed into human breast milk. However, it is distributed into the milk of lactating rats. Pioglitazone is not recommended for use by nursing mothers 1.

Pediatrics

Appropriate studies on the relationship of age to the effects of pioglitazone have not been performed in the pediatric population. Safety and efficacy have not been established 1.

Geriatrics

Placebo-controlled studies performed in approximately 500 patients 65 years of age or older have not demonstrated geriatrics-specific problems that would limit the use of pioglitazone in the elderly 1.

Pharmacogenetics

No pharmacokinetic data is available among various ethnic groups 1.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Ketoconazole

(concurrent use may decrease metabolism of pioglitazone 1)

Oral contraceptives, ethinylestradiol- and norethindrone-containing

(concurrent use may reduce plasma concentrations of both hormones 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and

Aspartate aminotransferase (AST [SGOT])

(during controlled clinical trials, reversible elevations greater than three times the upper limit of normal were observed in 0.26% of pioglitazone-treated patients versus 0.25% of placebo-treated patients; however, ALT elevations were not clearly related to pioglitazone 1)

Cholesterol, total and

High-density lipoproteins (HDL) and

Low-density lipoproteins (LDL)

(during clinical trials, increases in HDL-C were observed in patients with lipid abnormalities; no consistent changes were observed in LDL-C and total cholesterol 1)

Creatine phosphokinase levels (CPK)

(during controlled clinical trials, sporadic, transient elevations in CPK levels were observed. They resolved without clincal sequele, and the relationship to pioglitazine therapy is unknown.) 3

Hematocrit and

Hemoglobin concentration

(during clinical trials, the mean hemoglobin concentration declined by 2% to 4% in patients treated with pioglitazone; decreases have been attributed to dilutional effects of increased plasma volume observed with pioglitazone 1)

Triglycerides

(during clinical trials, mean decreases in triglycerides were observed 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

>> Diabetes mellitus, type 1 or

>> Diabetic ketoacidosis

(pioglitazone lowers plasma glucose concentrations only in the presence of insulin 1)

>> Hepatic function impairment

(pioglitazone should not be started in patients with clinical evidence of active liver disease or in patients with an alanine aminotransferase value greater than 2.5 times the upper limit of normal 1)

>> Hypersensitivity to pioglitazone 1

Risk-benefit should be considered when the following medical problem exists

>> Congestive heart failure

(use is not recommended in patients with New York Heart Association Class III and IV cardiac status because pioglitazone causes plasma volume expansion 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Glucose concentrations, fasting blood

(regular monitoring recommended to assess therapeutic efficacy 1)

>> Glycosylated hemoglobin determinations

(regular monitoring recommended to assess long-term glycemic control 1)

>> Liver function tests

(recommended if the patient develops symptoms, such as abdominal pain, anorexia, dark urine, fatigue, nausea, or vomiting, that are suggestive of hepatic dysfunction 1)

>> Transaminase values

(recommended prior to the start of therapy, every 2 months for the first year of therapy, and periodically thereafter; pioglitazone should not be initiated in patients exhibiting clinical evidence of active liver disease or ALT values greater than 2.5 times the upper limit of normal and should be discontinued if values become and remain greater than three times the upper limit of normal or if the patient develops jaundice 1)

Side/Adverse Effects

Note: Pioglitazone does not stimulate insulin secretion and, administered alone, is not expected to cause hypoglycemia. However, there is a potential for hypoglycemia when pioglitazone is administered in conjunction with insulin, metformin, or a sulfonylurea. 1

In all U.S. clinical trials, edema was more frequent after treatment with pioglitazone than placebo. The incidence of edema was 4.8% and 1.2% following treatment with pioglitazone and placebo, respectively. Edema occurred in 15.3% of patients who received combination therapy with insulin and pioglitazone versus 7% of patients who received combination therapy with insulin and placebo. Caution should be exercised when pioglitazone is administered to patients with edema 1.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Tooth disorders ¾incidence 5.3% 1

Incidence less frequent

Peripheral edema (swelling of feet or lower legs)¾incidence 4.8% in monotherapy studies 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Headache¾incidence 9.1% 1; myalgia (muscle soreness)¾incidence 5.4% 1; pharyngitis (sore throat)¾ incidence 5.1% 1; sinusitis (runny or stuffy nose)¾ incidence 6.3% 1; upper respiratory tract infection (cough; fever; runny or stuffy nose; sore throat)¾incidence 13.2% 1

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

During clinical trials, one patient took pioglitazone at a dose of 120 mg a day for 4 days followed by 180 mg for 7 days. The patient did not have any clinical symptoms during this period 1.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Pioglitazone (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to pioglitazone
Pregnancy¾Use of insulin alone is recommended during pregnancy for maintenance of blood glucose concentrations as close to normal as possible
Breast-feeding¾Not recommended for use by nursing mothers
Other medications, especially ketoconazole
Other medical problems, especially congestive heart failure, diabetic ketoacidosis, hepatic function impairment, or type 1 diabetes
Proper use of this medication

>> Importance of adherence to recommended regimens for diet, exercise, and glucose monitoring

May be taken with or without food

>> Proper dosing
Missed dose: Taking as soon as possible if remembered the same day; if dose is missed on one day, not doubling dose the following day
Precautions while using this medication

>> Reporting symptoms, such as abdominal pain, anorexia, dark urine, fatigue, jaundice, nausea, or vomiting, that are suggestive of hepatic dysfunction to physician immediately

>> Regular visits to physician to check progress and monitor liver function

>> Carefully following special instructions of health care team

Discussing use of alcohol

Not taking other medications unless discussed with physician

Getting counseling for family members to help the patient with diabetes; also, special counseling for pregnancy planning and contraception

Making travel plans that include readiness for diabetic emergencies and eating meals at the usual times, even with changing time zones

>> Preparing for and understanding what to do in case of diabetic emergency; carrying medical history and current medication list and wearing medical identification

>> Recognizing what brings on symptoms of hypoglycemia, such as using other antidiabetic medication; delaying or missing a meal; exercising more than usual; drinking significant amounts of alcohol; or illness, including vomiting or diarrhea

>> Recognizing symptoms of hypoglycemia: anxiety; behavior change similar to drunkenness; blurred vision; cold sweats; confusion; cool, pale skin; difficulty in concentrating; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nervousness; nightmares; restless sleep; shakiness; slurred speech; or unusual tiredness or weakness

>> Knowing what to do if symptoms of hypoglycemia occur, such as eating glucose tablets or gel, corn syrup, honey, or sugar cubes; drinking fruit juice, nondiet soft drink, or sugar dissolved in water; or injecting glucagon if symptoms are severe

>> Recognizing what brings on symptoms of hyperglycemia, such as not taking enough or skipping a dose of antidiabetic medication, overeating or not following meal plan, having a fever or infection, or exercising less than usual

>> Recognizing symptoms of hyperglycemia and ketoacidosis: blurred vision; drowsiness; dry mouth; flushed, dry skin; fruit-like breath odor; increased urination (frequency and volume); ketones in urine; loss of appetite; stomachache, nausea, or vomiting; tiredness; troubled breathing (rapid and deep); unconsciousness; and unusual thirst

>> Knowing what to do if symptoms of hyperglycemia occur, such as checking blood glucose and contacting a member of the health care team

Side/adverse effects

Signs of potential side effects, especially tooth disorders and peripheral edema

General Dosing Information

Management of type 2 diabetes should include nutritional counseling, weight reduction as needed, and exercise. These are not only important in the primary treatment of the disease but also to maintain the efficacy of the drug therapy. 3, 2

Diet/Nutrition

Food slightly delays the time to peak serum concentration but does not alter the extent of absorption. Pioglitazone may be taken without regard to meals. 1

Oral Dosage Forms

PIOGLITAZONE TABLETS

Usual adult dose

Antidiabetic agent¾
As monotherapy¾
Oral, initially 15 or 30 mg once daily without regard to meals. If the patient has an inadequate response to pioglitazone, the dose may be increased in increments up to 45 mg once daily 1, 2, 3.

In combination with insulin *¾
Oral, initially 15 or 30 mg once daily without regard to meals. When pioglitazone is initiated, the current insulin dose can be continued; however, if hypoglycemia occurs or if the plasma glucose concentration is 100 mg/dL or less, the dose of insulin should be decreased by 10% to 25% 1, 3.

In combination with metformin *¾
Oral, initially 15 or 30 mg once daily without regard to meals. When pioglitazone is initiated, the current metformin dose can be continued. The metformin dose is unlikely to require adjustment due to hypoglycemia 1, 3.

In combination with a sulfonylurea *¾
Oral, initially 15 or 30 mg once daily without regard to meals. When pioglitazone is initiated, the current sulfonylurea dose can be continued; however, if hypoglycemia occurs, the dose of the sulfonylurea should be decreased 1, 3.

Usual adult prescribing limits

45 mg of pioglitazone daily 1, 2, 3.

Doses greater than 30 mg once daily for combination therapy have not been studied in clinical trials. 3

Usual pediatric dose

Safety and efficacy have not been established 1, 2, 3.

Usual geriatric dose

See Usual adult dose.

Strength(s) usually available
U.S.¾15 mg (Rx)[Actos (lactose monohydrate NF) (hydroxypropylcellulose NF) (carboxymethylcellulose calcium NF) (magnesium stearate NF) 1, 3]

30 mg (Rx)[Actos (lactose monohydrate NF) (hydroxypropylcellulose NF) (carboxymethylcellulose calcium NF) (magnesium stearate NF) 1, 3]

45 mg (Rx)[Actos (lactose monohydrate NF) (hydroxypropylcellulose NF) (carboxymethylcellulose calcium NF) (magnesium stearate NF) 1, 3]

Canada¾15 mg (Rx)[Actos (lactose monohydrate) (hydroxypropylcellulose) (carboxymethylcellulose calcium) (magnesium stearate) 2]

30 mg (Rx)[Actos (lactose monohydrate) (hydroxypropylcellulose) (carboxymethylcellulose calcium) (magnesium stearate) 2]

45 mg (Rx)[Actos (lactose monohydrate) (hydroxypropylcellulose) (carboxymethylcellulose calcium) (magnesium stearate) 2]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) in a tightly closed container. Protect from moisture and humidity 1, 2, 3.

* Not included in Canadian product labeling.