Pioglitazone HCl

Zolid®

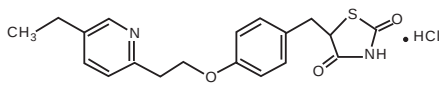
15mg, 30mg Tablets

Anti-Diabetes

DESCRIPTION

Pioglitazone (ZOLID®) is an oral antidiabetic agent used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes) that acts primarily by decreasing insulin resistance. Pioglitazone belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin or the α-glucosidase inhibitors.

Pioglitazone hydrochloride is chemically known as [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride and has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl. The structural formula is:



Pioglitazone hydrochloride

Formulation:

Pioglitazone (ZOLID®) is available for oral administration as:

1. Pioglitazone (ZOLID®) 15mg Tablets
   Each tablet contains:
   Pioglitazone…15mg
   (as hydrochloride)

2. Pioglitazone (ZOLID®) 30mg Tablets
   Each tablet contains:
   Pioglitazone…30mg
   (as hydrochloride)

CLINICAL PHARMACOLOGY

Mechanism of Action

Pioglitazone is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Pharmacokinetics

Absorption:

Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration for 3 to 4 hours, but does not alter the extent of absorption.

Distribution:

The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism:

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 and 3A4. Three of the six metabolites formed are active. The major circulating metabolite is M-IV (1-hydroxyethyl pioglitazone), which accounts for most of the drug-related material in human plasma and probably accounts for much of the therapeutic efficacy.

Elimination:

Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7L/hr.

Special Populations

Renal Insufficiency:

In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but with similar oral clearance of parent medicine. Thus free (unbound) pioglitazone concentration remains unchanged. Dose adjustment in patients with renal dysfunction is not recommended.

Hepatic Insufficiency:

Patients with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

Geriatric:

No clinically significant differences between elderly and young subjects were observed.

Pediatrics:

Pharmacokinetic data in the pediatric population are not available.

Gender:

The mean C_{max} and AUC values were increased 20% to 60% in females. Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Drug-Drug Relationships

Glipizide: Co-administration of pioglitazone and 5mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Metformin: Co-administration of a single dose of metformin (1000mg) and pioglitazone after 7 days did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of pioglitazone for 15 days followed by a single 7.5mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Nifedipine ER: In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

THERAPEUTIC INDICATIONS

Pioglitazone (ZOLID®) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).

Pioglitazone (ZOLID®) can also be taken alone as a monotherapy, or it can be used in combination with a sulfonylurea, metformin or a insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

DOSAGE AND ADMINISTRATION

Pioglitazone (ZOLID®) tablets are taken once daily with or without meals and should be taken about the same time everyday. However, skipping meals while taking this medicine is not advised. This can cause hypoglycemia.

Monotherapy

Pioglitazone (ZOLID®) monotherapy may be initiated at 15mg or 30mg once daily, increasing after four weeks to 45mg once daily, if greater therapeutic effect is needed.

Combination Therapy
Pioglitazone (ZOLID®) in combination with sulfonylureas, insulin or metformin may be initiated at 15mg or 30mg once daily. It may be possible to achieve metabolic control at a reduced dose of sulfonylurea, insulin or metformin. If there is a particular risk of hypoglycemia, pioglitazone can be introduced at a dose of 15mg. For patients already on insulin, pioglitazone should be introduced at a dose of 15mg once daily.

Maximum Recommended Dose
The dose of Pioglitazone (ZOLID®) should not exceed 45mg once daily since doses higher than 45mg once daily have not been studied.

Hepatic Impaired Patients
The intrinsic clearance of pioglitazone may be reduced in patients with hepatic disease. Dosage should start at 15mg and be increased cautiously.

ADVERSE REACTIONS
The adverse effects reported include:
- Upper respiratory tract infections
- Headache
- Sinusitis
- Myalgia
- Tooth disorder
- Diabetes mellitus aggravated
- Pharyngitis

There was also a tendency to modest weight gain. Some people may also experience anemia and fluid retention. These side effects do not happen in all people.
There was an increase in the occurrence of edema in the patients treated with pioglitazone and insulin compared to insulin alone. Pioglitazone plus insulin developed dyspnea at some point during therapy.

CONTRAINDICATIONS
Pioglitazone is contraindicated in patients with known hypersensitivity to thiazolidinediones or any component of this product.

WARNINGS
- **Cardiac Failure and Other Cardiac Effects**
  Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.
- Do not use Pioglitazone in patients with active bladder cancer.
- Use Pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of blood sugar control with Pioglitazone should be weighed against the unknown risks for cancer recurrence.

PRECAUTIONS
General: Pioglitazone exerts its antihyperglycemic effect only in the presence of insulin. Therefore, pioglitazone should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving pioglitazone in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Edema: Pioglitazone should be used with caution in patients with edema.

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit causing anemia. Hemoglobin monitoring is recommended if patients exhibit any signs or symptoms of anemia.

Ovulation: Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone. Thus, adequate contraception in premenopausal women should be recommended.

Hepatic effects: Therapy with pioglitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy. Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with pioglitazone and periodically thereafter.

Pediatrics: Since data is unavailable for pediatric patients, use of pioglitazone is not recommended.

Pregnancy: Pioglitazone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether pioglitazone is secreted in human milk. Because many drugs are excreted in human milk, pioglitazone should not be administered to a breast-feeding woman.

Drug Interactions
Ketoconazole: Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism *in vitro* at a concentration equal molar to pioglitazone. Pending the availability of additional data, patients receiving ketoconazole concomitantly with pioglitazone should be evaluated more frequently with respect to glycemic control. *Oral Contraceptives:* Administration of thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. Therefore, additional caution regarding contraception should be exercised in patients receiving pioglitazone and an oral contraceptive.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

AVAILABILITY
Pioglitazone (ZOLID®) 15mg Tablets are available in a blister pack of 2 x 7 tablets.

Pioglitazone (ZOLID®) 30mg Tablets are available in a blister pack of 2 x 7 tablets.

Keep out of reach of children.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph

REGISTRATION NUMBER:
Zolid Tablets 15mg: DR-XY33842
Zolid Tablets 30mg: DR-XY33381

DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION
Zolid Tablet 15mg:
Initial: 27 September, 2007
Amended: 18 July, 2012
Renewal: 05 December, 2012

Zolid Tablet 30mg:
Initial: 28 May, 2007
Renewal: 23 November, 2012

DATE OF REVISION OF PACKAGING INSERT 19 September, 2017.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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