Zolid™

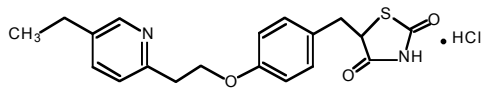
[Pioglitazone HCl]

Tablets 15mg, 30mg, 45mg

DESCRIPTION

ZOLID (Pioglitazone) 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

QUALITATIVE & QUANTITATIVE COMPOSITION

ZOLID (Pioglitazone) is available for oral administration as:

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

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

3. ZOLID Tablets 45mg
   Each tablet contains:
   Pioglitazone…45mg
   (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 is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. 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.

Oral Contraceptives: Co-administration of pioglitazone (45mg once daily) and an oral contraceptive (1mg norethindrone plus 0.035mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively.

Fexofenadine HCl: Co-administration of pioglitazone for 7 days with 60mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. Pioglitazone had no significant effect on fexofenadine pharmacokinetics.

Digoxin: Co-administration of pioglitazone with 0.25mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of pioglitazone for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. Pioglitazone has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Ranitidine HCl: Co-administration of pioglitazone for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. Pioglitazone showed no significant effect on ranitidine pharmacokinetics.

Atorvastatin Calcium: Co-administration of pioglitazone for 7 days with atorvastatin calcium 80mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65- 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Gemfibrozil: Concomitant administration of gemfibrozil (oral 600mg twice daily), an inhibitor of CYP2C8, with pioglitazone (oral 30mg) resulted in pioglitazone exposure (AUC0-24) being 226% of the pioglitazone exposure in the absence of gemfibrozil.

Rifampin: Concomitant administration of rifampin (oral 600mg once daily), an inducer of CYP2C8 with pioglitazone (oral 30mg) resulted in a decrease in the AUC of pioglitazone by 54%.

Ketoconazole: Co-administration of pioglitazone for 7 days with ketoconazole 200mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06-1.23) for C_{max} 1.34 (1.26-1.41) for AUC and 1.87 (1.71-2.04) for C_{min}.

THERAPEUTIC INDICATIONS

ZOLID (Pioglitazone) 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).

1. ZOLID (Pioglitazone) may be used along in type 2 diabetes metlitus as a second line therapy or
2. In combination with metformin or with a sulphonylurea only when
   - patients are unable to tolerate metformin and sulphonylurea combination therapy
   - patients are contraindicated to either metformin or sulphonylurea In such cases, the thiazolidinedione should replace which ever drug in the combination is poorly tolerated or contraindicated.

DOSAGE AND ADMINISTRATION

ZOLID (Pioglitazone) 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

ZOLID (Pioglitazone) 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

ZOLID (Pioglitazone) in combination with sulphonylureas, 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 sulphonylurea, 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 ZOLID (Pioglitazone) should not exceed 45mg once daily since doses higher than 45mg once daily have not been studied.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

ZOLID (Pioglitazone) should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema or signs and symptoms of CHF exacerbation.

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 components of this product.
- Initiation of pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated.

WARNINGS

Congestive Heart Failure:

- Thiazolidinediones cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone and after dose increases, the patient 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, the heart failure should be managed according to the current standard of care. Furthermore, discontinuation or dose reduction of drug must be considered.
- Pioglitazone is not recommended in patients with symtomatic heart failure. Initiation of this drug in patients with established NYHA Class III or IV heart failure is contraindicated.

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. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered.

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.
- Inadequate response to a combination of metformin and a sulphonylurea may indicate failing insulin release; the introduction of pioglitazone has a limited role in these circumstances and insulin treatment should not be delayed.

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: Since thiazolidinediones, including pioglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, pioglitazone should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure.

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit causing anemia. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. 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.

OVERDOSAGE

Patients have taken pioglitazone at higher than the recommended highest dose of 45mg daily. The maximum reported dose of 120mg/day for four days, then 180mg/day for seven days was not associated with any symptoms. Hypoglycemia may occur in combination with sulphonylureas or insulin. Symptomatic and general supportive measures should be taken in case of overdose.

STORAGE

Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

ZOLID (Pioglitazone) 15mg tablets are available in blister pack of 2 x 7's.
ZOLID (Pioglitazone) 30mg tablets are available in blister pack of 2 x 7's.
ZOLID (Pioglitazone) 45mg tablets are available in blister pack of 2 x 7's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

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

Getz pharma (PVT) LIMITED
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