Zolid®

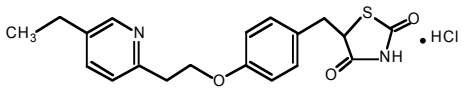
(Pioglitazone HCl)

ذولِڈ

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 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 AND QUANTITATIVE COMPOSITION

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, pioglitazone is rapidly absorbed, and peak plasma concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Steady state is achieved after 4–7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.

Distribution:

The estimated volume of distribution is 0.25 L/kg. Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99 %) in serum.

Metabolism:

Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified metabolites are active (M-II, M-III, and M-IV), concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis M-IV contribution to efficacy is approximately three-fold that of pioglitazone, whilst the relative efficacy of M-II is minimal.

Excretion:

Following oral administration of radio labeled pioglitazone, recovered label was mainly in feces (55%) and a lesser amount in urine (45%). The mean plasma elimination half-life of unchanged pioglitazone is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Special populations

Renal Insufficiency

In patients with renal insufficiency, plasma concentrations of pioglitazone and its metabolites are lower than with normal renal function, but oral clearance of parent substance is similar. Thus free (unbound) pioglitazone concentration is unchanged.

Hepatic Insufficiency

Total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone.

THERAPEUTIC INDICATIONS

ZOLID is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as;

Monotherapy

In patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

Dual oral therapy in combination with:

- Metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.
- Sulphonylurea, only in patients who show in tolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

Triple oral therapy in combination with:

Metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

DOSAGE AND ADMINISTRATION

ZOLID should be taken once daily without regard to meals.

Monotherapy

ZOLID monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15mg or 30mg once daily. For patients who respond inadequately to the initial dose of ZOLID, the dose can be increased in increments up to 45mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas

ZOLID in combination with a sulfonylurea may be initiated at 15mg or 30mg once daily. The current sulfonylurea dose can be continued upon initiation of ZOLID therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin

ZOLID in combination with metformin may be initiated at 15mg or 30mg once daily. The current metformin dose can be continued upon initiation of ZOLID therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ZOLID.

Insulin

ZOLID in combination with insulin may be initiated at 15mg or 30mg once daily. The current insulin dose can be continued upon initiation of ZOLID therapy. In patients receiving ZOLID

and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose
The dose of ZOLID should not exceed 45mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Renal insufficiency
Dose adjustment in patients with renal insufficiency is not recommended.

Adverse reaction
Including mono and combination therapy are the following:
Very Common

Hypoglycaemia, edema.

Common

Visual disturbances, upper respiratory tract infection, weight increase, hypoaesthesia, anemia, arthralgia, headache, haematuria, erectile dysfunction, flatulence, dizziness, blood creatine phosphokinase increase, bronchitis, back pain, dyspnoea, heart failure.

Rare

Sinusitis, flatulence, vertigo, fatigue, increased lactic dehydrogenase, appetite increased, hypoglycaemia, headache, glycosuria, proteinuria, sweating.

CONTRAINDICATIONS
Pioglitazone is contraindicated in patients with:
- hypersensitivity to the active substance or to any of the excipients.
- cardiac failure or history of cardiac failure (NYHA stages I to IV).
- hepatic impairment
- diabetic ketoacidosis.

Pregnancy:
The mechanism of Pioglitazone is unclear in pregnant women therefore Pioglitazone should not be used in pregnancy.

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

WARNING

CONGESTIVE HEART FAILURE
- Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some. After initiation of pioglitazone, and after dose increases, observe patients 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 standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered.
- Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established NYHA Class III or IV heart failure is contraindicated.

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.

Hematologic: Pioglitazone may cause decreases in hemoglobin and hematocrit.

Hepatic effects: Therapy with pioglitazone should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with pioglitazone should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with pioglitazone in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring.

Weight Gain: Dose related weight gain may occur with pioglitazone alone and in combination with other hypoglycemic agents.

Macular Edema: Macular edema may occur in diabetic patients who take pioglitazone or another thiazolidinedione. Some patients may have blurred vision or decreased visual acuity, but some patients may have diagnosed on routine ophthalmologic examination. Patients with diabetes should have regular eye exams by an ophthalmologist.

Fractures: An increased incidence of bone fracture is possible in female patients taking pioglitazone.

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

Gemfibrozil: When pioglitazone is given with gemfibrozil, an inhibitor of cytochrome P450 isoenzyme CYP2C8, there is a three fold increase in the area under the concentration –time curve (AUC) of pioglitazone , and a decrease in pioglitazone dose may be needed if it is given with gemfibrozil or similar CYP2C8.

Rifampicin: Pioglitazone dose may need to be increased when rifampicin, a potent inducer of cytochrome P450, is given with pioglitazone, as it halves the AUC of pioglitazone..

STORAGE
Store at 25^{O}C (Excursions permitted between 15 ^{O}C to 30 ^{O}C)
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
ZOLID (Pioglitazone) Tablets 15mg are available in blister pack of 14's.

ZOLID (Pioglitazone) Tablets 30mg are available in blister pack of 14's.

ZOLID (Pioglitazone) Tablets 45mg are available in blister pack of 14's.

Keep out of the 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.

Manufactured by:

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29-30/27, K.I.A., Karachi, Pakistan

Rev. Jun 10
L02-200004278