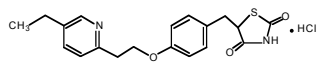
Pioglitazone HCl + Metformin HCl

ZolidPlus

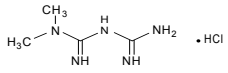
15mg + 500mg, 15mg + 850mg Film-Coated Tablets
Oral Hypoglycemic

DESCRIPTION
Pioglitazone and metformin HCl (Zolid Plus) is an advanced diabetes treatment that combines two important diabetes medications. Pioglitazone is an effective drug for reducing blood glucose if there is inadequate control on the conventional agents alone, and metformin HCl which lowers the amount of sugar produced by the liver.
Pioglitazone is chemically known as [(±)-5-[[4-[2-(5ethyl-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 HCl

Chemically metformin HCl is known as *N,N*-dimethylimidodicarbonimidic diamide hydrochloride and it is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. Metformin HCl has a molecular formula of $C_4H_{11}N_5$.HCl and the structural formula is:



Metformin HCl

FORMULATION
Pioglitazone+Metformin HCl (Zolid Plus) is available for oral administration as:

1. Pioglitazone+Metformin HCl (Zolid Plus)Tablets 15mg+500mg
   Each film-coated tablet contains:
   Pioglitazone (as hydrochloride)…15mg
   Metformin HCl…500mg

2. Pioglitazone+Metformin HCl (Zolid Plus)Tablets 15mg+850mg
   Each film-coated tablet contains:
   Pioglitazone (as hydrochloride)…15mg
   Metformin HCl…850mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Pioglitazone+Metformin HCl (Zolid Plus) combines 2 anti-diabetic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Pioglitazone: 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). It improves glycemic control by improving insulin sensitivity at key sites of insulin resistance namely adipose tissues, skeletal muscles and liver.
Insulin resistance is known to play a major role in the pathogenesis of type 2 diabetes.

Metformin HCl: Metformin HCl is an anti-hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Metformin HCl may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Pharmacokinetics
Absorption
Pioglitazone: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes with 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.

Metformin HCl: Metformin HCl is slowly and incompletely absorbed from the gastrointestinal tract. The absolute bioavailability of a single 500mg dose is reported to be about 50-60% given under fasting conditions. Food decreases the extent and slightly delays the absorption of metformin.

Distribution
Pioglitazone: 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.

Metformin HCl: Metformin HCl is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. The blood peak is lower than the plasma peak and appears at approximately the same time.

Metabolism
Pioglitazone: 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.

Metformin HCl: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Excretion
Pioglitazone: 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.

Metformin HCl: Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours.

Special Populations
Renal Insufficiency
Pioglitazone: 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.

Metformin HCl: In subjects with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency
Pioglitazone: 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.

Metformin HCl: No pharmacokinetics studies of metformin have been conducted in subjects with hepatic insufficiency.

THERAPEUTIC INDICATIONS
Pioglitazone+Metformin HCl (Zolid Plus) is indicated for patients with type 2 diabetes mellitus when single agent therapy is inadequate or for patients requiring combined or more intensive therapy.

DOSAGE AND ADMINISTRATION
The use of anti-hyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of pioglitazone 45mg and metformin 2550mg.
Selecting the starting dose of Pioglitazone+Metformin HCl (Zolid Plus) should be based on the patient's current regimen of pioglitazone and/or metformin.
Pioglitazone+Metformin HCl (Zolid Plus) should be given in divided daily doses with meals to reduce the gastrointestinal side effects associated with metformin.

Starting dose for patients inadequately controlled on metformin monotherapy
Based on the usual starting dose of pioglitazone (15-30mg daily), Pioglitazone+Metformin HCl (Zolid Plus) may be initiated at either the 15mg+850mg or 15mg+850mg tablet once or twice daily, and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients who initially responded to pioglitazone monotherapy and require additional glycemic control
Based on the usual starting doses of metformin (500mg twice daily or 850mg daily), Pioglitazone+Metformin HCl (Zolid Plus) may be initiated at either the 15mg+500mg twice daily or 15mg+850mg tablet once daily and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients switching from combination therapy of pioglitazone plus metformin as separate tablets
Pioglitazone+Metformin HCl (Zolid Plus) may be initiated with either the 15mg+500mg or 15mg+850mg tablet based on the dose of pioglitazone and metformin already being taken.

ADVERSE REACTIONS
In general treatment with Pioglitazone+Metformin HCl (Zolid Plus) was well tolerated. The possible side effects include:

Combination therapy:
Common: Anaemia, visual disturbance, weight increased, arthralgia, headache, haematuria, erectile dysfunction.

Uncommon: Flatulence.
Individual active substances of the fixed dose combination:

Pioglitazone:
Common: Upper respiratory tract infection and hypoesthesia.
Uncommon: Sinusitis and insomnia.

Metformin HCl:
Most common: Taste disturbance, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite.
Uncommon: Decrease in Vitamin B12 absorption and serum levels, lactic acidosis.

CONTRAINDICATIONS
Pioglitazone+Metformin HCl (Zolid Plus) is contraindicated in patients with:
- Hypersensitivity to pioglitazone, metformin HCl or any component of the product.
- Cardiac failure or history of cardiac failure (NYHA Class III or IV).

- Hepatic impairment or evidence of active liver disease.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock.
- Acute alcohol intoxication, alcoholism.
- Renal failure or renal dysfunction (creatinine clearance <60mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction and septicemia.

WARNINGS

Pioglitazone:

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 sign 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 symptomatic heart failure. Initiation of this drug in patients with essential NYHA Class III or IV heart failure is contraindicated.
- Do not use Pioglitazone in patients with active bladder cancer.
- Use Pioglitazone with caution in patients with prior history of bladder cancer. The benefits of blood sugar control with Pioglitazone should weighed against the unknown risks for cancer recurrence.

Metformin HCl:

Lactic acidosis is rare, but serious metabolic complication that can occur due to metformin accumulation during treatment. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. The onset of lactic acidosis often is accompanied only by non-specific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis.

PRECAUTIONS

Pioglitazone:

General:
- Pioglitazone exerts its anti-hyperglycemic 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.

Cardiac Failure and Other Cardiac Effects: Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other anti-diabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care.

Ovulation: Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. Thus, adequate contraception in premenopausal women should be recommended while taking Pioglitazone+Metformin HCl (Zolid Plus).

Hypoglycemia: Patients receiving pioglitazone in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycaemia.

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

Hepatic Effects: Therapy with pioglitazone + metformin HCl 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+Metformin HCl (Zolid Plus) should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with pioglitazone + metformin HCl 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.

Metformin HCl:
- Lactic acidosis is a very rare, but serious, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately.
- Intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, Pioglitazone+Metformin HCl (Zolid Plus) should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.
- Pioglitazone+Metformin HCl (Zolid Plus) should be promptly discontinued when cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxemia occur in patients.
- Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving Pioglitazone+Metformin HCl (Zolid Plus). Since impaired hepatic function has been associated with some cases of lactic acidosis, Pioglitazone+Metformin HCl (Zolid Plus) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.
- Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with hypoglycemic agents (such as sulfonylureas or insulin) or ethanol. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

Drug Interactions

Pioglitazone:

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response.

Oral Contraceptives: Administration of another 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.

Metformin HCl:

Cationic drugs:

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine) careful patient monitoring and dose adjustment of Pioglitazone+Metformin HCl (Zolid Plus) and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Furosemide: Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance.

Nifedipine: Co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Others: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytonin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to a patient receiving Pioglitazone+Metformin HCl (Zolid Plus) the patient should be closely observed to maintain adequate glycemic control.

STORAGE CONDITIONS

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

AVAILABILITY

1. Pioglitazone + Metformin HCl (Zolid Plus) Tablets 15mg+500mg are available in blister pack of 28's.
2. Pioglitazone + Metformin HCl (Zolid Plus) Tablets 15mg+850mg are available in blister pack of 14's.

CAUTION

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

Keep out of reach of children.

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

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