Zoliget™

زولیگیٹ

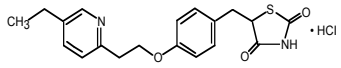
(Pioglitazone + Glimepiride)

Tablets 15mg+2mg, 30mg+2mg & 30mg+4mg

DESCRIPTION

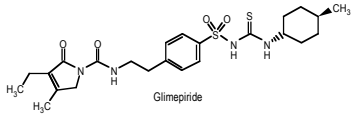
ZOLIGET (Pioglitazone+Glimepiride) combines two antihyperglycemic agents to improve glycemic control with type 2 diabetes: pioglitazone hydrochloride, a member of the thiazolidinedione class and glimepiride, a member of the sulfonylurea class.

Chemically pioglitazone is [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl) ethoxy] phenyl] methyl]-2, 4-] thiazolidinedione monohydrochloride. The molecular formula is $C_{19}H_{20}N_2O_3S.HCl$ and the structural formula is:



Pioglitazone HCl

Chemically glimepirideis 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea. The molecular formula is $C_{24}H_{34}N_4O_5S$ and the structural formula is:



Glimepiride

QUALITATIVE & QUANTITATIVE COMPOSITION

ZOLIGET (Pioglitazone+Glimepiride) is available for oral administration as:

1. ZOLIGET Tablets 15mg+2mg
   Each tablet contains:
   Pioglitazone HCl USP equivalent to Pioglitazone… 15mg
   Glimepiride USP… 2mg
2. ZOLIGET Tablets 30mg+2mg
   Each tablet contains:
   Pioglitazone HCl USP equivalent to Pioglitazone… 30mg
   Glimepiride USP… 2mg
3. ZOLIGET Tablets 30mg+4mg
   Each tablet contains:
   Pioglitazone HCl USP equivalent to Pioglitazone… 30mg
   Glimepiride USP… 4mg

CLINICAL PHARMACOLOGY

Mechanism of Action

ZOLIGET (Pioglitazone+Glimepiride) is a combination of two antihyperglycemic agents to improve glycemic control in patients with type 2 diabetes.

Pioglitazone:

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 sulfonylurea, 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.

Glimepiride:

The primary mechanism of action of glimepiride appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects (e.g., reduction of basal hepatic glucose production and increased peripheral tissue sensitivity to insulin and glucose uptake) may also play a role in the activity of glimepiride. However, as with other sulfonylurea, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacokinetics

Pioglitazone:

Pioglitazone is rapidly absorbed after oral doses. Peak plasma concentrations are obtained within 2 hours and bioavailability exceeds 80%. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolized by cytochrome P450 isoenzymes CYP3A4 and CYP2C9 to both active and inactive metabolites. It is excreted in urine and feces and has a plasma half-life of up to 7 hours. The active metabolites have a half-life of up to 24 hours.

Glimepiride:

After oral administration glimepirideis completely absorbed from the GI tract. The oral bioavailability is approximately 100%. Peak plasma concentrationsoccur in 2-3 hours. More than 99% of the drug is bound to plasma proteins. Glimepiride is completely metabolized by oxidative biotransformation into two main metabolites, a hydroxy derivative and a carboxy derivative.

The elimination half-life ($t_{1/2}$) after multiple doses is about 9 hours. Approximately 60% of dose is eliminated in the urine and 40% in the feces.

Special Populations

Pioglitazone:

Hepatic Impairment: 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. Therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceeds 2.5 times the upper limit of the normal.

Glimepiride:

Renal Impairment: A single-dose clinical study of glimepiride showed that glimepiride serum levels decreased with the decrease in renal function. However, metabolites serum levels (mean AUC values) increased. The apparent terminal half-life ($t_{1/2}$) for glimepiride does not change, while the half-lives for metabolites increased as renal function decreased. Mean urinary excretion of metabolites as percent of dose, however, decreased.

Elderly:

Pioglitazone:

In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, butAUC values are slightly higher and the terminal half-life valueslightly longer than for younger subjects. These changes were notof a magnitude thatwould be considered clinically relevant.

Glimepiride:

Comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤65 years and those >65 years was performed ina study using a dosingregimen of 6 mg daily. There were nosignificant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about13% lower than thatfor the youngerpatients; the mean weight adjusted clearance for the older patients was about 11% higher than that for the younger patients.

THERAPEUTIC INDICATIONS

ZOLIGET (Pioglitazone+Glimepiride) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and a sulfonylurea or whose diabetes is not adequately controlled with glimepiride alone, or for those patients who have initially responded to pioglitazonealone and require additional glycemic control.

DOSAGE AND ADMINISTRATION

The use of antihyperglycemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. Failure to follow an appropriate dosage regimen may precipitate hypoglycemia.

Dosage Recommendations

Selecting the starting dose of ZOLIGET (Pioglitazone+Glimepiride) should be basedon the patient's current regimen of pioglitazone and/or sulfonylurea. Those patients who may be more sensitive to antihyperglycemic drugs should be monitored carefully during dose adjustment. After initiation of ZOLIGET (Pioglitazone+Glimepiride), patients should be carefully monitered for adverse events related to fluid retention. It is recommended that a single dose of ZOLIGET (Pioglitazone+Glimepiride) be administered once daily with the first main meal.

Starting Dose for Patients Currently on Pioglitazone Monotherapy

Therapy should be started with 15mg+2mg & 30mg+2mg tablet once daily followed by titration to reach the required dose.

Starting Dose for Patients Currently on Glimepiride Monotherapy

Therapy should be started with 15mg+2mg, 30mg+2mg & 30mg+4mg tablet once daily followed by titration to reach the required dose.

Starting Dose for Patients Switching from Combination Therapy of Pioglitazone Plus Glimepiride as Separate Tablets

Therapy should be started with 15mg+2mg, 30mg+2mg & 30mg+4mg tablet once daily as per the doses of each already being taken.

Starting Dose for Patients Currently on a Different Sulfonylurea Monotherapy or Switching from Combination Therapy of Pioglitazone Plus a Different sulfonylurea

Therapy should be started with 15mg+2mg or 30mg+2mg once daily followed by titration to reach the required dose.

Maximum Recommended Dose

ZOLIGET (Pioglitazone+Glimepiride) Tablets are available as a 15mg pioglitazone + 2mg glimepiride or a 30mg pioglitazone + 2mg glimepiride or a 30mg pioglitazone + 4mg glimepiride formulation for oral administration. The maximum recommended daily dose for pioglitazone is 45mg and the maximum recommended daily dose for glimepiride is 8mg. ZOLIGET (Pioglitazone+Glimepiride) should therefore not be given more than once daily at any of the tablet strengths.

Special Patient Populations

In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage of ZOLIGET (Pioglitazone+Glimepiride) should be conservative to avoid hypoglycemic reactions. These patients should be started at 1mg of glimepiride prior to prescribing ZOLIGET (Pioglitazone+Glimepiride). During initiation of ZOLIGET (Pioglitazone+Glimepiride) therapy and any subsequent dose adjustment, patients should be observed carefully for hypoglycemia. Therapy with ZOLIGET (Pioglitazone+Glimepiride) 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. The lowest approved dose of ZOLIGET (Pioglitazone+Glimepiride) therapy should be prescribed to patients with type 2 diabetes and systolic dysfunction only after titration from 15mg to 30mg of pioglitazone has been safelytolerated. If subsequent dose adjustment is necessary, patients should be carefully monitored for weight gain, edema, or signs and symptoms of CHF exacerbation.

ADVERSE REACTIONS

The more common side effects for the combination are anxiety, bladder pain, bloody or cloudy urine, blurred vision, chills, cold sweats, coma, confusion, cool pale skin, depression, difficult/burning or painful urination, fast heartbeat, frequent urge to urinate, headache, increased hunger, increased weight, lower back or side pain, nausea, nervousness, nightmares, seizures, shakiness, slurred speech, swelling of feet or lower legs, unusual tiredness or weakness, cough, ear congestion, hoarseness, joint pain, loss of voice, nasal congestion, tooth disorder, voice changes. The less common side effects for the combination include accidental injury, loss of appetite, pain or swelling in arms or legs without any injury, pale skin, stomach pain, troubled breathing with exertion, unusual bleeding or bruising, vomiting, weight loss, yellow eyes or skin, allergic skin reactions. Other side effects include upper respiratory tract infection, myalgia, diabetes aggravated, asthenia. In isolated cases, impairment of liver function (e.g., with cholestasis and jaundice) as well as hepatitis, which may also lead to liver failure have been reported. Cases of hyponatremia have been reported most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The hematologic adverse reactions include leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia and pancytopenia.

CONTRAINDICATIONS

Pioglitazone+Glimepiride combination is contraindicated in patients:

- With known hypersensitivity to pioglitazone, glimepiride or any other component of the product.
- With diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- With antihypertensive effect in the presence of insulin; therefore this drug should not be used in patients of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- With moderate to severe heart failure or liver problems.
- This medication is not recommended for use in pregnancy, nursing mothers and in pediatric patients.

WARNINGS

CONGESTIVE HEART FAILURE

- Thiazolidinediones, including pioglitazone, which is a component of ZOLIGET (Pioglitazone + Glimepiride), cause or exacerbate congestive heart failure in some patients. After initiation of ZOLIGET (Pioglitazone+Glimepiride), 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 of ZOLIGET (Pioglitazone+Glimepiride) must be considered.
- ZOLIGET (Pioglitazone+Glimepiride) is not recommended in patients with symptomatic heart failure. Initiation of ZOLIGET (Pioglitazone+ Glimepiride) in patients with established NYHA Class III or IV heart failure is contraindicated.

PRECAUTIONS

- 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.
- All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemic episodes. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of glimepiride. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Debilitated patients, malnourished patients and patients

with adrenal, pituitary, renal or hepatic insufficiency are particularly susceptible to the hypoglycemic action of sulfonylurea and should therefore be carefully monitored. The dosage of glimepiride should be carefully adjusted in these patients.

- Pioglitazone may cause decline in hematocrit value along with the decline in mean hemoglobin values by 2%-4% causing anemia. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematological clinical effects.
- In patients with type 2 diabetes (mean duration of diabetes 9.5 years), an increased incidence of bone fracture in female patients taking pioglitazone is observed. The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.
- Alcohol ingestion, severe or prolonged exercise, deficient caloric intake or use of more than one antidiabetic agent may predispose patients to the development of hypoglycemia.
- When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with glimepiride or even use insulin monotherapy.
- The patient's fasting blood glucose and HbA1c must be measured periodically to determine the minimum effective dose of pioglitazone+glimepiride combination for the patient.
- Liver enzyme monitoring is recommended prior to initiation of therapy with pioglitazone+glimepiride combination in all patients and periodically thereafter as per the clinical judgment of the health care professional.

Drug Interactions
Pioglitazone hydrochloride:
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.

Ketoconazole: Co-administration of pioglitazone for 7 days with ketoconazole 200mg administered twice daily resulted in a ratio of 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}.

Atorvastatin Calcium: Co-administration of pioglitazone for 7 days with atorvastatin calcium 80mg once daily resulted in a ratio of 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 ratio of 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 & Rifampin: 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.

Glimepiride:
The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including non-steroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors and beta-adrenergic blocking agents. Due to the potential drug interaction between these drugs and glimepiride, the patient should be observed closely for hypoglycemia when these drugs are co-administered. Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics and isoniazid. Due to the potential drug interaction between these drugs and glimepiride, the patient should be observed closely for loss of glycemic control when these drugs are co-administered.

Aspirin: Co-administration of aspirin (1g three times daily) and glimepiride led to a 34% decrease in the mean glimepiride AUC and, therefore, a 34% increase in the mean CL/f. The mean C_{max} had a decrease of 4%.

Propanolol: Concomitant administration of propranolol (40mg three times daily) and glimepiride significantly increased C_{max}, AUC, and $t_{1/2}$ of glimepiride by 23%, 22%, and 15%, respectively and it decreased CL/f by 18%. If beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Miconazole: A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. There is a potential interaction of glimepiride with inhibitors (e.g., fluconazole) and inducers (e.g., rifampicin) of cytochrome P4502C9.

OVERDOSAGE
Pioglitazone hydrochloride:
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Glimepiride:
Symptoms
After ingestion of an overdosage hypoglycemia may occur, lasting from 12 to 72 hours and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Management
Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water with activated charcoal (adsorbent) and sodium-sulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

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

HOW SUPPLIED
1. ZOLIGET (Pioglitazone+Glimepiride) Tablets 15mg+2mg are available in blister pack of 14's.
2. ZOLIGET (Pioglitazone+Glimepiride) Tablets 30mg+2mg are available in blister pack of 14's.
3. ZOLIGET (Pioglitazone+Glimepiride) Tablets 30mg+4mg are available in blister pack of 14'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.

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