Glibetic
(Pioglitazone + Glimepiride)
Tablets 15mg+2mg

گلائبیٹک ٹیبلٹس
(پائیوگلیٹازون + گلیمی پرائیڈ)

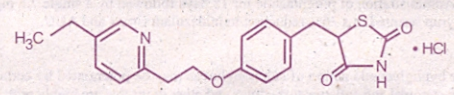
Glibetic Plus
(Pioglitazone + Glimepiride)
Tablets 30mg+2mg

گلائبیٹک پلس ٹیبلٹس
(پائیوگلیٹازون + گلیمی پرائیڈ)

Glibetic Forte
(Pioglitazone + Glimepiride)
Tablets 30mg+4mg

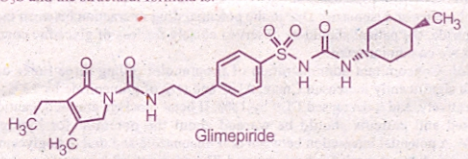
گلائبیٹک فورٹ ٹیبلٹس
(پائیوگلیٹازون + گلیمی پرائیڈ)

DESCRIPTION
Glibetic (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. The structural formula is:



Pioglitazone HCl

Chemically glimepiride is 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl] sulphonyl]-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
Product Complies Manufacturer's Spec.
Glibetic (Pioglitazone + Glimepiride) is available for oral administration as:

1. GLIBETIC Tablets 15mg+2mg
Each tablet contains: Pioglitazone (as HCl) Manufacturer's Spec..... 15mg
Glimepiride USP 2mg

2. GLIBETIC Plus Tablets 30mg+2mg
Each tablet contains: Pioglitazone (as HCl) Manufacturer's Spec..... 30mg
Glimepiride USP 2mg

3. GLIBETIC Forte Tablets 30mg+4mg
Each tablet contains: Pioglitazone (as HCl) Manufacturer's Spec..... 30mg
Glimepiride USP 4mg

CLINICAL PHARMACOLOGY
Mechanism of Action
GLIBETIC (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. Pioglitazone is a potent and highly selective agonist for peroxisome proliferatoractivated receptor-gamma (PPARg). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR 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 sulfonylureas, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacokinetics
Pioglitazone:
After oral administration, in the fasting state pioglitazone is rapidly absorbed and peak plasma concentrations are obtained within 2 hours. Pioglitazone is more than 99% bound to plasma proteins. It is extensively metabolized by cytochrome P450 isoenzymes CYP3A4 and CYP2C8 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 glimepiride is completely absorbed from the GI tract. The oral bioavailability is approximately 100%. Peak plasma concentrations occur in 2-3 hours. More than 99.5% of the drug is bound to plasma proteins. Glimepiride is completely metabolized by oxidative biotransformation into two main metabolites, a hydroxy derivative and a carboxyl 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 Insufficiency: Impaired hepatic function (Child-Pugh Grade B/C) has an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentration 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 Insufficiency: A single-dose clinical study of glimepiride showed that glimepiride serum levels decreased with the decrease in renal function. However, metabolites serum levels (means 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.

THERAPEUTIC INDICATIONS
GLIBETIC (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 sulfonylurea alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

DOSAGE & ADMINISTRATION
General
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
Starting dose of GLIBETIC (Pioglitazone + Glimepiride) should be based on 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. It is recommended that a single dose of GLIBETIC (Pioglitazone + Glimepiride) be administered once daily with the first main meal.

Starting dose for patients currently on pioglitazone monotherapy
Based on the usual starting doses of glimepiride (1mg or 2mg once daily), and pioglitazone 15mg or 30mg, GLIBETIC (Pioglitazone + Glimepiride) may be initiated at 15mg+2mg one daily, and adjusted after assessing adequacy of therapeutic response.

Starting dose for patients currently on glimepiride monotherapy
Based on the usual starting dose of pioglitazone (15mg or 30mg daily), GLIBETIC (Pioglitazone + Glimepiride) may be initiated at 15mg+2mg once daily, and adjusted after assessing adequacy of therapeutic response.

Starting dose for patients switching from combination therapy of pioglitazone plus glimepiride as separate tablets
GLIBETIC (Pioglitazone + Glimepiride) may be initiated with 15mg+2mg tablet based on the dose of pioglitazone and glimepiride already being taken. Patients who are not controlled with 15mg of pioglitazone in combination with glimepiride should be carefully monitored when switched to GLIBETIC (Pioglitazone + Glimepiride).

Starting dose for patients currently on a different sulfonylurea monotherapy or switching from combination therapy of pioglitazone plus a different sulphonylurea
No exact dosage relationship exists between glimepiride and the other sulfonylurea agents. Therefore, based on the maximum starting dose of 2mg glimepiride, GLIBETIC (Pioglitazone + Glimepiride) should be limited initially to a starting dose of 15mg+2mg once daily and adjusted after assessing adequacy of therapeutic response. Any change in diabetic therapy should be undertaken with care and appropriate monitoring as change in glycemic control can occur. Patients should be observed carefully for hypoglycemia (1-2 weeks) when being transferred to GLIBETIC (Pioglitazone + Glimepiride), especially from longer half-life sulphonylureas due to potential overlapping of drug effect.

Maximum Recommended Dose
GLIBETIC (Pioglitzone + Glimepiride) tablets are available as a 15mg pioglitazone plus 2mg glimepiride or a 30mg pioglitazone plus 2mg glimepiride or a 30mg pioglitazone plus 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. GLIBETIC (Pioglitazone + Glimepiride) should therefore not be given more than once daily in 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 GLIBETIC (Pioglitazone + Glimepiride) should be conservative to avoid hypoglycemic reactions. These patients should be started at 1mg of glimepiride prior to prescribing GLIBETIC (Pioglitazone + Glimepiride). During initiation of GLIBETIC (Pioglitazone + Glimepiride) therapy and any subsequent dose adjustment, patients should be observed carefully for hypoglycemia.

Therapy with GLIBETIC (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 GLIBETIC (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 safely tolerated. 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 upper respiratory tract infection, accidental injuries, combined edema/peripheral edema, hypoglycemia, weight increase, headache, urinary tract infection, diarrhea, nausea and pain in limb. Anaemia was reported in 2% patients treated with pioglitazone and sulphonylurea.

Pioglitazone:
Most clinical adverse event were similar between groups treated with pioglitazone in combination with sulphonylurea and those treated with pioglitazone monotherapy. Other adverse events reported are myalgia, tooth disorder, diabetes mellitus and pharyngitis respectively.

Glimepiride:
Adverse events reported other than hypoglycemia are headache, nausea, dizziness, and asthenia. Gastrointestinal Reactions: Vomiting, gastrointestinal pain and diarrhea have been reported with glimepiride. Dermatologic Reactions: Allergic skin reactions e.g., pruritus, erythema, urticaria and morbilliform or maculopapular eruptions. Metabolic Reactions: Hyponatremia has been reported with glimepiride and all other sulphonylureas. Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia and pancytopenia have been reported with sulfonylureas. Other Reactions: Changes in accommodation and/or blurred vision may occur with the use of glimepiride.

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 antihyperglycemic 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 active liver disease.
- 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 GLIBETIC (Pioglitazone + Glimepiride), cause or exacerbate congestive heart failure in some patients. After initiation of GLIBETIC (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 GLIBETIC (Pioglitazone + Glimepiride) must be considered.
- GLIBETIC (Pioglitazone + Glimepiride) is not recommended in patients with symptomatic heart failure. Initiation of GLIBETIC (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 instruction 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 sulfonylureas 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 hegmoglobin 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, especially in the 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 per the clinical judgement of the health care professional.

Drug Interactions

Pioglitazone Hydrochloride:
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.
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 uncharged pioglitazone of 1.14 (1.06 - 1.23) for Cmax, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for Cmin.
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 Cmax, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for Cmin. For unchanged atorvastatin,the ratio of least square mean (90% CI) values were 0.77 (0.66 - 0.90) for Cmax, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for Cmin.
Midazolam: Administration of pioglitazone for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam Cmax and AUC.

Glimepiride:
General: The hypoglycemia action of sulphonylureas 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, nicotine 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.
Propranolol: Concomitant administration of propranolol (40mg three times daily) and glimepiride significantly increased Cmax, AUC and t1/2 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 hypoglycemia 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.

STORAGE

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

Keep out of reach of children.
To be sold on a prescription of registered medical practitioner.

HOW SUPPLIED

1. **Glibetic** (Pioglitazone + Glimepiride) Tablets 15mg+2mg are available in blister packs of 14's.
2. **Glibetic** Plus (Pioglitazone + Glimepiride) Tablets 30mg+2mg are available in blister packs of 14's.
3. **Glibetic** Forte (Pioglitazone + Glimepiride) Tablets 30mg+4mg are available in blister packs of 14's.

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

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو روشنی، نمی اور گرمی سے محفوظ 30°C سے کم درجہ حرارت پر رکھیں۔
صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فراہم کی جائے۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Manufactured by: Maple Pharmaceuticals (Pvt) Ltd.
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Affiliated with: Maple Pharmaceuticals Inc. Canada.

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