Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Cationic drugs: Certain medications used concomitantly with metformin may increase the risk of lactic acidosis. Cationic drugs that are eliminated by renal tubular secretions (e.g: amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, ranitidine, or vancomycin) may decrease metformin elimination by competing form common renal tubular transport systems. Hence, careful patient monitoring and dose adjustment of metformin and/or interfering cationic drug is recommended.

Vitamin B12: Metformin may result in suboptimal oral vitamin B12 absorption by competitively blocking the calcium dependent binding of the intrinsic factor vitamin B12 complex to its receptor. The reaction very rarely results in pernicious anemia that is reversible with discontinuation of metformin or with vitamin B12, supplementation.

Nifedipine: Nifedipine appears to enhance the absorption of metformin, it increases plasma metformin Cmax and AUC by 20% and 9% respectively, and increases the amount of metformin excreted in the urine. Metformin has minimal effects on nifedipine.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller,respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Thiazide: Interactions between thiazide diuretics and oral antidiabetic agents decreases insulin sensitivity thereby leading to glucose intolerance and hyperglycaemia, thus leading to a loss of diabetic control. Hence diabetic patients should be monitored closely.

Other: Concomitant administration of angiotensin enzyme inhibitors (captopril, enalapril), other antidiabetic drugs (insulin, acarbose) beta blockers,fluconozole,histamine (H2) receptor antagonist, monoamine oxidase inhibitors (MAOIs), sulphonamides and non-steroidal anti inflamatory agents increases sensitivity to insulin and potentiation of blood glucose lowering effect and thus ,in some instances, hypoglycaemia may occur . Dosage of Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets may need to be reduced.

Patients receiving corticosteroids, phenothiazines,thyroid products,phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid should be closely monitored for loss of diabetic control when therapy is instituted or discontinued. When such drugs are administered to a patient receiving Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets, the patient should be closely observed to maintain adequate glycaemic control.

OVERDOSAGE

Glimepiride

An overdosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

Pioglitazone

During controlled clinical trials, one case of overdose with pioglitazone was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied clinical symptoms during this period. In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

Metformin

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

STORAGE

Store below 30°C.

PACKAGING INFORMATION:

Pioglitazone Hcl with Glimepiride and Metformin Hcl Sustained Release Tablets - Blister of 10 tablets

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, INDIA.

B3135-01

ILET BP आई लेट - बी पी

Pioglitazone Hcl with Glimepiride and Metformin Hcl Sustained Release Tablets

COMPOSITION

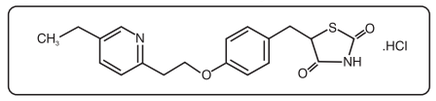
ILET BP1 आई लेट - बी पी १
Each uncoated bi-layered tablet contains Pioglitazone Hydrochloride IP Equivalent to Pioglitazone.....15 mg
Glimepiride IP.....1 mg
Metformin Hydrochloride IP 500 mg
(As sustained release form)
Colour: Lake of Quinoline Yellow

ILET BP2 आई लेट - बी पी २
Each uncoated bi-layered tablet contains Pioglitazone Hydrochloride IP Equivalent to Pioglitazone.....15 mg
Glimepiride IP.....2 mg
Metformin Hydrochloride IP 500 mg
(As sustained release form)
Colour: Lake of Sunset Yellow

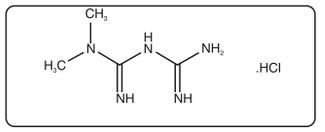
1) The drug should not be used as first line of therapy for diabetes.
2) Advice for healthcare professionals

Warning : 1) Patients with active bladder cancer or with a history of bladder cancer, and those with uninvestigated haematuria, should not receive pioglitazone
2) Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 months of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequantely to treatment (eg, reductio in glycosylated haemoglobin HbA1c).
3) Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assaeeed in individuals: age, current or past history of smoking, exposure to same occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region.
4) Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.

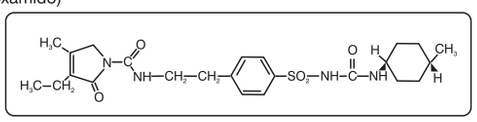
Pioglitazone Hcl, [(±)-5-[[4-[2-(5-ethyl-2 pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride



Metformin Hcl, (N,N -dimethylimidodicarbonimidic diamide hydrochloride)



Glimepiride, 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1carboxamido) ethyl]phenyl]sulfonyl]-3-(trans-4 methylcyclohexyl)urea



PHARMACOLOGY

Pharmacodynamics:

Glimepiride

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta-cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin. In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2-3 hours after single oral doses of glimepiride. The effects of glimepiride on HbA1c, fasting plasma glucose, and post-prandial glucose have been assessed in clinical trials.

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 proliferator-activated receptor-(PPAR-). 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. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values.

Metformin HCl

Metformin is an oral antihyperglycaemic drug used in the management of type 2 diabetes. It improves glucose tolerance in patients with type 2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to sulphonylureas, thiazolidinediones, or-glucosidase inhibitors. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulphonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains

unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption:

Metformin HCl

Metformin is an oral antihyperglycaemic drug used in the management of type 2 diabetes. It improves glucose tolerance in patients with type 2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose.Metformin is not chemically or pharmacologically related to sulphonylureas, thiazolidinediones, or -glucosidase inhibitors. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulphonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulinIn healthy subjects, the intra-and inter-individual variabilities of glimepiride pharmacokinetic parameters were 15-23% and 24-29%, respectively.

Pioglitazone:

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 to 3 to 4 hours, but does not alter the extent of absorption.

Metformin extended release:

The absolute bioavailability of a metformin 500-mg tablet given under fasting conditions is approximately 50 60%. Following a single oral dose of metformin extended release; Cmax is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release.

At steady state, the AUC and Cmax are less than dose proportional for extended release within the range of 500 mg to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively.

The extent of metformin absorption (as measured by AUC) from extended release at a 2000 mg once-daily dose is similar to the same total daily dose administered as immediate release tablets 1000 mg twice daily. After repeated administration of extended release, metformin did not accumulate in plasma. Within subject variability in Cmax and AUC of metformin from extended release is comparable to that with immediate release.

Although the extent of metformin absorption (as measured by AUC) from the extended release tablet increased by approximately 50% when given with food, there was no effect of food on Cmax and Tmax of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of extended release.

INDICATIONS AND USAGE

Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets, used as a once per day, are indicated as an adjunct to diet and exercise, to lower blood glucose. It is indicated as second-line therapy when diet, exercise, single agents and dual combination therapy do not result in adequate glycaemic control in patients with type 2 diabetes. Further, it is also indicated in drug naïve patients, showing no symptoms, with an HbA1c of >9.0% at the time of diagnosis.

DOSAGE AND ADMINISTRATION

Dosage should be individualized on the basis of both effectiveness and tolerability while not exceeding the maximum recommended daily dose of individual components. Maximum recommended dose of glimepiride is 8 mg; pioglitazone is 45 mg and of metformin extended release is 2000 mg. The combination should be given once daily with meals and should be started at a low dose. The initial recommended dose is one tablet of Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 1 or Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 2 once daily.

In case of inadequate glycaemic control with above mentioned doses, consider up titrating to one tablet of Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 3, Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets FORTE 1 or Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets FORTE 2.

Dosage should not exceed three tablets per day of Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 1 or Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 2, and two tablets of Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets 3, Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets FORTE 1 or Pioglitazone HCl with Metformin HCl Sustained release and Glimepiride tablets FORTE 2.

CONTRAINDICATIONS

1. Initiation in patients with established New York Heart Association (NYHA) Class III or Ivheart failure is contraindicated.
2. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels (1.5mg/dL) [males],1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia.
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
4. Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.
5. Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to glimepiride. Do not use this product in patients who have a history of an allergic reaction to sulfonamide derivatives.
6. Known hypersensitivity to this product or any of its components.

WARNINGS AND PRECAUTIONS

Drug Interactions

Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control.

The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme(ACE) inhibitors, H2 receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenyramidol, guanethidine, fluconazole, sulfinpyrazone, tetracyclines, clarithromycin, disopyramide, quinolones, and those drugs that are highly protein bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics(e.g., epinephrine, albuterol, terbutaline), and isoniazid. When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for hypoglycemia

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-lowering effect. Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion. The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

Miconazole: A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

Cytochrome P450 2C9 Interactions: There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

Aspirin: In a study, healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 1 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Co-administration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride Cmax.

Cimetidine and Ranitidine: In a study, healthy subjects received either a single 4 mg dose of glimepiride alone, glimepiride with ranitidine (150 mg twice daily for 4 days; glimepiride was administered on Day 3), or glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on Day 3). Coadministration of cimetidine or ranitidine with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

Propranolol: In a study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 or each study period, a single 2 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14 day washout period. Concomitant administration of propranolol and glimepiride significantly increased glimepiride Cmax, AUC, and T 1/2 by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/f by 18%. The recovery of M1 and M2 from urine was not changed

Warfarin: In a study, healthy subjects received 4 mg of glimepiride daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting glimepiride and on Day 4 of glimepiride administration. The concomitant administration of glimepiride did not alter the pharmacokinetics of R- and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

Strong CYP2C8 Inhibitors: An inhibitor of CYP2C8 (e.g., gemfibrozil) significantly increases the exposure (area under the serum concentration-time curve or AUC) and half-life of pioglitazone. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors.

CYP2C8 Inducers: An inducer of CYP2C8 (e.g.,rifampin) may significantly decrease the exposure (AUC) of pioglitazone. Therefore, if an inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response without exceeding the maximum recommended daily dose of 45 mg for pioglitazone.