GLIMITAB MP Tablets
Glimepiride, Pioglitazone & Metformin SR Tablets

COMPOSITION

Glimitab MP-1
Each tablet contains:
- Glimepiride 1 mg
- Metformin Hydrochloride sustained-release 500 mg
- Pioglitazone Hydrochloride 15 mg

Glimitab MP-2
Each tablet contains:
- Glimepiride 2 mg
- Metformin Hydrochloride sustained-release 500 mg
- Pioglitazone Hydrochloride 15 mg

CLINICAL PHARMACOLOGY

Glimitab MP contains three oral anti-hyperglycemic drugs glimepiride, pioglitazone and metformin hydrochloride used in the management of type-2 diabetes (NIDDM).

Pharmacodynamics

**Glimepiride**: The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.

**Pioglitazone** selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated haemoglobin in the bloodstream.

**Metformin** decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

The combination of glimepiride, pioglitazone and metformin sustained-release complements each other and provides better glycemic control in the management of type-2 diabetes and probably in the prevention of its associated macrovascular and microvascular complications.

Pharmacokinetics

Absorption

**Glimepiride**: After oral administration, glimepiride is completely absorbed from the GI tract. Studies have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. When glimepiride was given with meals, the mean Tmax (time to reach Cmax) was slightly increased (12%) and the mean Cmax and AUC (area under the curve) were slightly decreased (8% and 9%, 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 [3 to 4 hours], but does not alter the extent of absorption.

**Metformin sustained 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 sustained-release, Cmax is achieved within 4-8 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. Both high and low fat meals had the same effect on the pharmacokinetics of extended release.

**Distribution**

**Glimepiride:** After intravenous dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg). Protein binding was greater than 99.5%.

**Pioglitazone:** The mean apparent volume of distribution (Vd/F) of pioglitazone following single dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. 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 sustained release:** Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 μg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

**Metabolism**

**Glimepiride:** Glimepiride is completely metabolized by oxidative biotransformation. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 II C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.

**Pioglitazone:** Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC. Urinary 6(beta)-hydroxycortisol/cortisol ratios measured in patients treated with pioglitazone showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

**Metformin sustained release:** Metabolism studies with metformin sustained-release have not been conducted. However, intravenous single-dose studies in normal subjects demonstrate that metformin immediate release does not undergo hepatic metabolism or biliary excretion.

**Excretion**

**Glimepiride:** When 14 C-glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted
for about 70% of that recovered in feces. No parent drug was recovered from urine or feces.

**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 7 L/hr.

**Metformin sustained release:** Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

**INDICATIONS**

Glimitab MP Tablets are indicated once daily, as an adjunct to diet and exercise, to lower blood glucose. It is indicated as second-line therapy when diet, exercise, and the single agents or dual therapy do not result in adequate glycemic control in patients with type-2 diabetes.

**DOSAGE & ADMINISTRATION**

Dosage should be individualized on the basis of both effectiveness and tolerability while not exceeding the maximum recommended daily dose [which is for glimepiride=8mg; pioglitazone=45mg; metformin sustained-release=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 Glimitab MP once daily. Dosage should not exceed 3 tablets per day of Glimitab MP-1 or Glimitab MP-2.

**CONTRAINDICATIONS**

- Renal disease or renal dysfunction, as suggested by serum creatinine levels ≥1.5 mg/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 septicemia.
- Hepatic Impairment: clinical evidence of active liver disease or serum transaminase levels (ALT) ≥2.5 times the upper limit of normal.
- Congestive heart failure requiring pharmacologic treatment.
- Known hypersensitivity to this product or any of its components.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function.

**WARNING & PRECAUTIONS**

**Congestive Heart Failure & other cardiac effects:**

Thiazolidinediones, including pioglitazone, which is a component of Glimitab MP, can cause fluid retention in some patients when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. The administration of oral hypoglycemic drugs (tolbutamide) has been reported to be associated with increased cardiovascular mortality as compared to treatment
with diet alone or diet plus insulin. In view of close similarities between the oral hypoglycemic drugs, this warning also applies for glimepiride. After initiation of Glimitab MP, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). Heart failure should be managed according to the current standards of care and discontinuation or dose reduction of Glimitab MP must be considered.

Lactic acidosis
Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation when used alone or in combination with other antihyperglycemic agents; when it occurs, it is fatal in approximately 50% of cases. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications.

Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis, metformin should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable, prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hepatic Effects
In postmarketing experience with pioglitazone, reports of hepatitis and of hepatic enzyme elevations have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Hence it is recommended that patients treated with Glimitab MP undergo periodic monitoring of liver enzymes.

The decision whether to continue the patient on therapy with Glimitab MP should be guided by clinical judgment pending laboratory evaluations.

Monitoring of renal function
Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Glimitab MP.

Before initiation of therapy with Glimitab MP and at least annually thereafter, renal function should be assessed. Glimitab MP should be discontinued if there is evidence of renal impairment.

Use of intravascular iodinated contrast materials:
Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to
acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, **Glimitab MP** should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

**Hypoxic states**
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients receiving **Glimitab MP** therapy, the drug should be promptly discontinued.

**Macular Edema**
Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. It is not known whether there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye examinations by an ophthalmologist.

**Fractures**
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.

**Hypoglycemia**
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 other hypoglycemic agents or alcohol. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to hypoglycemic effects.

Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Patients receiving pioglitazone in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose may be necessary.

**Alcohol intake**
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 metformin.

**Loss of control of blood glucose**
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold the diabetic regime and temporarily administer insulin. The oral antidiabetic therapy may be reinstituted after the acute episode is resolved.

**Type 1 diabetes**
Both pioglitazone and metformin exert their antihyperglycemic effect only in the presence of insulin. Therefore, **Glimitab MP** should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
**Edema**
In clinical studies, the incidence of edema has been reported more frequently in patients treated with pioglitazone than in placebo-treated patients and appears to be dose related.

**Weight Gain**
Dose related weight gain was observed with pioglitazone alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

**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 Glimitab MP.

**Hematologic**
Glimitab MP may cause decreases in hemoglobin and hematocrit. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects.

**Pregnancy Category C**
Abnormal blood glucose levels during pregnancy are associated with the higher incidence of congenital abnormalities. Most experts suggest insulin be used to maintain the blood glucose levels as close to normal as possible.

**Lactation**
Studies in lactating rats have shown that metformin and pioglitazone is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted on nursing mothers. Also Glimepiride should not be used by breast-feeding mothers. Hence, the use of Glimitab MP is contraindicated in lactating mothers, and if the diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

**Pediatric use**
Safety and effectiveness of Glimitab MP in pediatric patients have not been established.

**Geriatric use**
Metformin is known to be excreted by the kidneys, and because risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Glimitab MP should be used only in patients with normal renal function. Because aging is associated with reduced renal function, the use of Glimitab MP should be used with caution as age increases. Care should be taken in the dose selection and regular renal function should be monitored.

**DRUG INTERACTIONS**
**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, digoxin, morphine, procainamide, quinidine, ranitidine, or vancomycin) may decrease metformin elimination by competing for common renal tubular transport systems. Hence, careful patient monitoring and dose adjustment of metformin/cationic drug is recommended.
Miconazole (systemic route, oromucosal gel) and Phenylbutazone (systemic route): Increases hypoglycemic effect of glimepiride.

**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.

**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 which is reversible with discontinuation of metformin and supplementation with vitamin B12.

**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.

**Danazol:** If the use of this active substance cannot be avoided, the patient's urine and blood glucose must be monitored. It may be necessary to adjust the dose of Glimitab MP during and after treatment with danazol.

**Salicylates:** If salicylates are administered in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control.

**Thiazide:** Interactions between thiazide diuretics and oral antidiabetic agents decreases insulin sensitivity thereby leading to glucose intolerance and hyperglycemia. Hence diabetic patients should be monitored closely.

**CYP2C8 inhibitors/ inducers:** An enzyme inhibitor of CYP2C8 (e.g. gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (e.g. rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started/stopped during treatment with pioglitazone, changes in diabetes treatment may be needed.

**Oral Contraceptives:** Administration of pioglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduces the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. Also, oral contraceptives can cause hyperglycemia. Therefore, additional caution regarding contraception should be exercised in patients receiving pioglitazone and an oral contraceptive.

**Other:** Concomitant administration of ACE inhibitors (captopril, enalapril), other antidiabetic drugs (insulin, acarbose) beta-blockers, fluconazole, monoamine oxidase inhibitors (MAOIs), sulphonamides and NSAIDs, increases sensitivity to
insulin and potentiate the blood glucose lowering effect and may in some instances cause hypoglycemia. Dosage of **Glimitab MP** 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 administered to a patient receiving **Glimitab MP**.

**UNDESIRABLE EFFECTS**

**Glimepiride:** Glimepiride appears to be associated with a low incidence of hypoglycemia. Glimepiride may have the potential to produce adverse cardiovascular effects; however glimepiride has been established agent for the treatment of type-2 diabetes for a number of years without adverse cardiovascular effects.

**Pioglitazone:** Adverse events such as edema, headache, upper respiratory tract infection, myalgia, sinusitis, and pharyngitis have been reported with pioglitazone therapy. Cases of anemia have been reported infrequently in patients treated with pioglitazone.

**Metformin sustained-release:** Nausea, diarrhea, abdominal pain, constipation, vomiting, metallic taste in mouth have been reported with metformin therapy. These reactions are generally dose related and disappear when the dose is reduced.

**OVERDOSAGE**

**Glimepiride:** Overdosage of sulphonylureas, including glimepiride, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid I.V. injection of concentrated glucose solution (20 to 30 %). This must be followed by the infusion of more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels within normal limits.

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

**Metformin:** 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, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

**PRESENTATION**

**Glimitab MP-1** is available in a strip of 10 tablets

**Glimitab MP-2** is available in a strip of 10 tablets

**STORAGE**

Store in a cool and dry place.