Glimitab-M 1mg/2mg Tablets

1. Composition

Each tablet contains:

Glimepiride	1mg/2mg
Metformin SR	500mg

2. Dosage form and strength

Glimitab M-1 is available in a strip of 10 tablets

Glimitab M-2 is available in a strip of 10 tablets

3. Clinical particulars

3.1 Therapeutic indication

Glimitab M is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type-2 diabetes who are already treated with a combination of glimepiride and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to glimepiride alone and require additional glycaemic control.

3.2 Posology and method of administration

General dosage should be individualized on the basis of both effectiveness and tolerance. The combination should be given once daily with meals and should be started at a low dose. The initial recommended dose is one tablet once daily with breakfast or first main meal of the day.

Starting dose for patients inadequately controlled on metformin monotherapy Glimitab M-1 or Glimitab M-2 may be initiated once daily, and gradually titrated after assessing the therapeutic response.

Starting dose for patients who initially responded to glimepiride monotherapy and require additional glycemic control Based on the initial starting dose of glimepiride (1 or 2 mg), Glimitab M-1 or Glimitab M-2 may be initiated once daily, and gradually titrated after assessing the therapeutic response.

Starting dose for patients switching from combination therapy of glimepiride plus metformin as separate tablets Glimitab M-1 or Glimitab M-2 may be initiated based on the dose of glimepiride and metformin already being taken.

Maximum Recommended Dose:

The maximum recommended dose for glimepiride is 8 mg daily. The maximum recommended daily dose for metformin sustained-release is 2000 mg in adults.

3.3 Contraindication

- GLIMITAB is not suitable for the treatment of insulin-dependent (type I) diabetes mellitus (e.g., for the treatment of diabetics with a history of ketoacidosis), of diabetic ketoacidosis, or of diabetic precoma or coma.
- GLIMITAB must not be used in patients hypersensitive to glimepiride, other sulfonylureas, other sulphonamides, or to any of the excipients (risk of hypersensitivity reactions).
- No experience has been gained concerning the use of GLIMITAB in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of renal or hepatic function, change-over to insulin is indicated, not least to achieve optimal metabolic control.

3.4 Special warnings and precautions for use

Cardiac effects: -The administration of oral hypoglycaemic 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 hypoglycaemic drugs, this warning also applies for glimepiride.

Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with glimepiride and metformin combination therapy; 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 and congestive heart failure.

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 haemodialysis is recommended to correct the acidosis and remove the accumulated metformin.

Hypoglycaemia: All sulphonylurea drugs are capable of producing severe hypoglycaemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycaemic episodes.

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 glycaemic 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.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake, while receiving metformin.

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 azotaemia. When such events occur in patients on metformin therapy, the drug should be promptly discontinued.

Haemolytic anaemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to haemolytic anaemia. Since glimepiride is a sulfonylurea agent, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.

Over dosage: Overdosages of sulfonylureas, including glimepiride, can produce hypoglycaemia. Mild hypoglycaemic 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 hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid IV injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycaemia may recur after apparent clinical recovery. Lactic acidosis is a rare, but serious, metabolic complication that can occur if metformin accumulates during treatment due to overdosing. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

3.5 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 hypoglycaemic 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 anaemia 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 glimepiride and metformin during and after treatment with danazol.

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

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

Other: Concomitant administration of angiotensin enzyme inhibitors (captopril, enalapril), other antidiabetic drugs (insulin, acarbose) beta-blockers, fluconozole, monoamine oxidase inhibitors (MAOIs), sulphonamides and NSAIDs, increases sensitivity to insulin and

potentiates blood glucose lowering effect and may in some instances, cause hypoglycaemia. Patients receiving estrogens or oral contraceptives, phenytoin, quinolones should be closely monitored for loss of diabetic control**.**

3.6 Use in special population

- Pediatric: Safety and effectiveness of glimepiride and metformin combination in Pediatric patients have not been established
- Geriatric: Aging is associated with reduced renal function, glimepiride and metformin combination should be used with caution in the elderly.
- Liver impairment: should be administered with extreme caution in patients with impaired liver function. It is advised to consult your doctor to make a suitable adjustment in dosage and/or time-interval between two dosages.
- Renal failure: 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, glimepiride and metformin should be used only in patients with normal renal function.
- Pregnancy and lactation: 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. The use of glimepiride and metformin combination is not recommended for use in pregnancy.

  Studies in lactating rats show that metformin 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 glimepiride and metformin combination is not recommended for use in lactating mothers, and if the diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

3.7 Effects on ability to drive and use machine

No data available.

3.8 Undesirable effects

Gastrointestinal disturbances: Nausea, diarrhoea, abdominal pain, constipation, vomiting and metallic taste in mouth may occur. These reactions are generally dose related and disappear when the dose is reduced.

Dermatological effects: Rash, pruritus, urticaria, erythema & flushing.

Miscellaneous: Headache and dizziness.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia, and pancytopenia have been reported with sulfonylureas, including glimepiride.

Metabolic Reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Hypoglycaemia: Glimepiride appears to be associated with a low incidence of hypoglycaemia. Although Glimepiride has the potential to produce adverse cardiovascular effects, glimepiride has been an established agent for the treatment of type-2 diabetes for a number of years without producing adverse cardiovascular effects.

3.9 Overdose

There is limited experience of overdose with Glimitab M Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

4. Pharmacological properties

4.1 Mechanism of action

The mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin. Glimepiride likely binds to ATP-sensitive potassium channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Membrane depolarization stimulates calcium ion influx through voltage-sensitive calcium channels. This increase in intracellular calcium ion concentration induces the secretion of insulin.

Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Hence, the combination of glimepiride and metformin sustained-release complements each other and provides better glycaemic control in management of type-2 diabetes and probably in the prevention of its associated macrovascular and microvascular complications.

4.2 Pharmacodynamics properties

Glimepiride, like glyburide and glipizide, is a "second-generation" sulfonylurea agent.

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) 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.

4.3 Pharmacokinetic properties

Glimepiride is completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 2 to 3 hours, and it is highly protein bound. The drug is extensively metabolised to two main metabolites, a hydroxy derivative and a carboxy derivative. The half-life after multiple doses is about 9 hours. About 60% of a dose is eliminated in the urine and 40% in the faeces.

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in a cool and dry place.