Sitagliptin & Metformin Hydrochloride 50 mg/500 mg and 50 mg/1000 mg Tablet

Description
Glipita® M is a combination of two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride. Sitagliptin is an highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme that act as incretin enhancer. Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Mode of Action
By inhibiting the DPP-4 enzyme, Sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type II diabetes and in normal subjects. Sitagliptin demonstrates high selectivity for DPP-4 and does not inhibit closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin reduces hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis, and stimulates intracellular glycogen synthesis by acting on glycogen synthase. In muscle, it increases insulin sensitivity, improving peripheral glucose uptake and utilization. Metformin also delays intestinal glucose absorption. Unlike sulfonylureas, metformin does not produce hypoglycemia 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 daylong plasma insulin response may actually decrease.

Indications
Glipita® M is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus to improve glycemic control when the single agent alone does not provide adequate glycemic control or when appropriate.

Dosage and Administration
The dosage of Glipita® M should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

Glipita® M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. The starting dose of Glipita® M should be based on the patient's current regimen.

The recommended starting dose in patients NOT currently treated with metformin is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.

The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of Glipita® M is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.
Co-administration of Glipita® M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

No studies have been performed specifically examining the safety and efficacy of Glipita® M in patients previously treated with other oral antihyperglycemic agents and switched to Glipita® M. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

**Use in Elderly**

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Sitagliptin/Metformin HCl combination should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

**Contraindications**

Sitagliptin/Metformin HCl combination is contraindicated in patients with:

- renal disease or renal dysfunction, e.g., 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;
- acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma;
- history of a serious hypersensitivity reaction to Sitagliptin/Metformin HCl combination or Sitagliptin such as anaphylaxis or angioedema.

This combination drugs should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

**Special Warnings and Precautions**

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Sitagliptin/Metformin HCl combination; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia.

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin/Metformin HCl combination. After initiation of Sitagliptin/Metformin HCl combination, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin/Metformin HCl combination should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin/Metformin HCl combination.

Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin/Metformin HCl combination should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Metformin and sitagliptin are known to be substantially excreted by the kidney. 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 Sitagliptin/Metformin HCl combination.

In the elderly, Sitagliptin/Metformin HCl combination should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function.

**Drug Interactions**

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood
concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study.

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Glipita® M is recommended.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Sitagliptin/Metformin HCl combination the patient should be closely observed to maintain adequate glycemic control.

Use during Pregnancy and Lactation

Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies in pregnant women with Sitagliptin/Metformin HCl combination or its individual components; therefore, the safety of Sitagliptin/Metformin HCl combination in pregnant women is not known. Sitagliptin/Metformin HCl combination should be used during pregnancy only if clearly needed.

- **Sitagliptin**: Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

- **Metformin hydrochloride**: Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Adverse Effects

The most common adverse reactions reported in > 5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache. Nasopharyngitis was the only adverse reaction reported in > 5% of patients treated with sitagliptin monotherapy. Hypoglycemia was also reported more commonly in patients treated with the combination of Sitagliptin and sulfonylurea, with or without Metformin, than in patients given the combination of placebo and sulfonylurea, with or without Metformin. The most common established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.
Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

**Pharmaceutical Precautions**
Keep out of the reach of children. Store below 30°C. Keep in the original package in a cool & dry place in order to protect from light and moisture.

**Commercial Pack**

**Glipita® M 50/500 Tablet:** Box containing 30 tablets in 3X10's blister strip. Each film coated tablet contains Sitagliptin Phosphate INN equivalent to 50 mg of Sitagliptin and Metformin Hydrochloride BP 500 mg.

**Glipita® M 50/1000 Tablet:** Box containing 30 tablets in 3X10’s blister strip. Each film coated tablet contains Sitagliptin Phosphate INN equivalent to 50 mg of Sitagliptin and Metformin Hydrochloride BP 1000 mg.

Manufactured by

BEXIMCO PHARMACEUTICALS LTD.
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