

Glazita M

(Sitagliptin Phosphate U.S.P. + Metformin HCl B.P.)

گلیزیٹا ایم
دسٹی گلیپٹن فاسفیٹ یو.ایس. پی. +
میٹفورمن ہائیڈروکلورائیڈ بی. پی.

COMPOSITION

Each film coated tablet contains 50 mg Sitagliptin + 500 mg Metformin.
Each film coated tablet contains 50 mg Sitagliptin + 1000 mg Metformin.

CLINICAL PHARMACOLOGY

Mechanism of Action: Glazita M is a combination of two antidiabetic medications with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and Metformin hydrochloride, a member of the biguanide class.

Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4.

Metformin: Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, 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. Unlike sulfonylureas, Metformin does not produce hypoglycemia 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.

PHARMACOKINETICS

The results of a bioequivalence study in healthy subjects demonstrated that the Sitagliptin and Metformin 50 mg + 500 mg and 50 mg + 1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of Sitagliptin and Metformin hydrochloride as individual tablets.

Absorption: Sitagliptin: The absolute bioavailability of Sitagliptin is approximately 87%. Coadministration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics of Sitagliptin.

Metformin hydrochloride: The absolute bioavailability of a Metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Food decreases the extent of and slightly delays the absorption of Metformin.

Distribution: Sitagliptin: The fraction of Sitagliptin reversibly bound to plasma proteins is low (38%).
Metformin hydrochloride: Metformin is negligibly bound to plasma proteins.

Metabolism: Sitagliptin: Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Metformin hydrochloride: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion: Sitagliptin: Following administration of an oral Sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal t_{1/2} following a 100 mg oral dose of Sitagliptin was approximately 12.4 hours.

Metformin hydrochloride: 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.

INDICATIONS AND USAGE

Glazita M is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Sitagliptin and Metformin is appropriate.

Important Limitations of Use: Glazita M should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Initial combination therapy or maintenance of combination therapy 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. Glazita M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to Metformin. Glazita M must not be split or divided before swallowing.

The starting dose of Glazita 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. 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 Glazita M is 50 mg Sitagliptin + 1000 mg Metformin hydrochloride twice daily.

Patients treated with an insulin secretagogue or insulin: Coadministration of Glazita 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. Any change in therapy of type 2 diabetes should be under taken with care and appropriate monitoring as changes in glycemic control can occur.

ADVERSE REACTIONS

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.

DRUG INTERACTIONS

Coadministration of multiple doses of Sitagliptin (50 mg) and Metformin (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either Sitagliptin or Metformin in patients with type 2 diabetes.

Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients as the risk of lactic acidosis may increase.

Cationic Drugs: 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.

Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs: 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 the patient should be closely observed to maintain adequate glycemic control. In healthy volunteers, the pharmacokinetics of Metformin and propranolol, and Metformin and ibuprofen were not affected when co-

administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Nifedipine: Nifedipine appears to enhance the absorption of Metformin. Metformin had minimal effects on nifedipine.

WARNINGS AND PRECAUTIONS

Lactic acidosis: Warn against excessive alcohol intake. Sitagliptin/Metformin is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.

Vitamin B12 deficiency: Metformin may lower Vitamin B12 levels. Measure hematologic parameters annually.
Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of therapy, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin and Metformin 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 combination tablet.

Hypersensitivity reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue medicine, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Renal Impairment: 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 and Metformin combination tablet.

Hepatic Impairment: Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin and Metformin combination tablet should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Surgical Procedures: Use of Sitagliptin and Metformin combination tablet should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women with Sitagliptin and Metformin combination tablet or its individual components.

Geriatric: Because Sitagliptin and Metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, Sitagliptin and Metformin combination should be used with caution as age increases.

Pediatric: Safety and effectiveness of Sitagliptin and Metformin combination in pediatric patients under 18 years have not been established.

Nursing Mothers: No studies in lactating animals have been conducted. Caution should be exercised when Sitagliptin and Metformin combination is administered to a nursing woman.

CONTRAINDICATIONS

Glazita M is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Hypersensitivity to Metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to Sitagliptin such as anaphylaxis or angioedema.

OVERDOSAGE

Sitagliptin: 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 as indicated by the patient's clinical status.

Sitagliptin is modestly dialyzable. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

Metformin hydrochloride: Hypoglycemia 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. Hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdose is suspected

PRESENTATION

Glazita M 50mg + 500mg Tablet : 2x7's/pack.
Glazita M 50mg + 1000mg Tablet : 2x7's/pack.

DOSAGE

As directed by the physician.

INSTRUCTIONS

Store below 30°C.
Protect from sunlight and moisture.
Keep out of reach of children.

Detailed prescribing information is available on request.

Manufactured by:
AsianContinental (Pvt.) Ltd.
D-32, S.I.T.E. II, Super Highway,
Karachi-Pakistan.



An ISO Certified Company

LFT/047/01

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

صوبہ ادنیٰ سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔