Glytec-M Tablets

گلائی ٹیک۔ایم گولیاں

(سیٹاگلپٹن فاسفیٹ/میٹفورمن ہائیڈروکلورائیڈ)

(Sitagliptin Phosphate USP/ Metformin HCl USP)

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels, anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5mcg/mL [see Warnings and Precautions]. Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
Steps to reduce the risk of and manage metformin-associated lactic acidosis in these highrisk groups are provided in the full prescribing information [see Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, and Use in Specific Populations]. If metformin-associated lactic acidosis is suspected, immediately discontinue **Glytec-M** Tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see Warnings and Precautions].

COMPOSITION: Each film coated tablet contains:
Sitagliptin Phosphate monohydrate USP equivalent to Sitagliptin ... 50mg
Metformin HCl USP ... 500mg/1000mg. (Innovator's Specification)

PHARMACOLOGY: MECHANISM OF ACTION: Sitagliptin: Sitagliptin inhibits dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of the active intact hormones are increased by Sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.
Metformin hydrochloride: Metformin is an anti-hyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral anti-hyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS: Sitagliptin is absorbed from the gastrointestinal tract, with a peak plasma concentration occurring about 1 to 4 hours after an oral dose, and a bioavailability of about 87%. Because co-administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics, Sitagliptin may be administered with or without food. It undergoes minimal metabolism, mainly by the cytochrome P450 isoenzymes CYP3A4, and to a lesser extent by CYP2C8. About 79% of the dose excreted unchanged in the urine. Renal excretion of Sitagliptin involves active tubular secretions; it is a substrate for organic anion transporter3 and P-glycoprotein. Its terminal half life is almost 32 hours. Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half life is reported to range from about 2 to 6 hour. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS: For adult patients with type 2 diabetes mellitus: Glytec-M is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. **Glytec-M** is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. **Glytec-M** is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. **Glytec-M** is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control.

CONTRA-INDICATIONS: Sitagliptin/Metformin HCl is contraindicated in patients with: Hyper sensitivity to active or any of the excipient of the product, Severe renal impairment (GFR below 30ml/min), acute metabolic acidosis, including lactic acidosis, diabetic ketoacidosis. Diabetic pre-coma. Acute conditions with the potential to alter renal function such as: Dehydration, severe infection, shock, intravascular administration of iodinated contrast agents. Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure, recent myocardial infarction, shock, hepatic impairment; acute alcohol intoxication, alcoholism; Breast-feeding.

DOSAGE AND ADMINISTRATION: The dosage of **Glytec-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 100mg sitagliptin and 2000mg metformin.
Glytec-M should generally be given twice daily with meals, with gradual dose escalation, to resuce the gastrointestinal (GI) side effects due to metformin.
For patients inadequately controlled on maximal tolerated dose of metformin monotherapy: For patients not adequately controlled on metformin alone, the usual starting dose should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose) plus the dose of metformin already being taken.
For patients switching from co-administration of sitagliptin and metformin: For patients switching from co-administration of sitagliptin and metformin, **Glytec-M** should be initiated at the dose of sitagliptin and metformin already being taken.
For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea: The dose should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken. When **Glytec-M** is used in combination with a sulphonylurea, alower dose of sulphonylurea may be required to reduce the risk of hypoglycemia.

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For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist: The dose should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken.
For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin: The dose should provide sitagliptin dosed as 50mg twice daily (100mg total daily dose) and a dose of metformin similar to the dose already being taken. When **Glytec-M** is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycemia. All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.
Special populations: Renal impairment: No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] = 60ml/min). **Glytec-M** should not be used in patients with moderate or severe renal impairment (glomerular filtration rate [GFR] < 60ml/min).
Hepatic impairment: Glytec-M must not be used in patients with hepatic impairment.

OVERDOSAGE: A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is hemodialysis. Approximately 13,5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis. 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.

WARNINGS AND PRECAUTIONS: General: Sitagliptin/Metformin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
Acute pancreatitis: If pancreatitis is suspected, Sitagliptin/Metformin and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin/Metformin should not be restarted. Caution should be exercized in patients with a history of pancreatitis.
Lactic acidosis: Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe vomiting, diarrhoea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.
Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Sitagliptin/Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued during conditions with the potential to alter renal function.
Hypoglycemia: Patients receiving Sitagliptin/Metformin in combination with a sulphonylurea or with insulin may be at risk for hypoglycemia.
Bullous pemphigoid: If bullous pemphigoid is suspected, Sitagliptin/Metformin should be discontinued.
Surgery: Sitagliptin/Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.
Administration of iodinated contrast agent: Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in Metformin accumulation and an increased risk of lactic acidosis. Sitagliptin/Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.
Pregnancy: Sitagliptin/Metformin should not be used during pregnancy.
Nursing Women: Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin/Metformin tablet must therefore not be used in women who are breast-feeding.

DRUG INTERACTIONS: Cationic drugs; Careful patient monitoring and dose adjustment of Sitagliptin/Metformin tablet and/or the interfering drug is recommended in patients who are taking cationic medications (e.g., cimetidine, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin), that are excreted via the proximal renal tubular secretory system. Carbonic anhydrase inhibitors; Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) 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 treated with Sitagliptin/Metformin tablet, as the risk of lactic acidosis may increase. 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 to a patient receiving Sitagliptin/Metformin tablet the patient should be closely observed to maintain adequate glycemic control. Furosemide; Pharmacokinetic parameters of both compounds were affected by co-administration. Nifedipine; Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin/Metformin tablet is recommended

ADVERSE REACTIONS: Common: hypoglycaemia, nausea, flatulence, vomiting. **Uncommon:** somnolence, diarrhea, constipation, upper abdominal pain, pruritus. **Rare:** thrombocytopenia.
Frequency not known: angioedema, rash, urticaria, cutaneous vasculitis, exfoliative skin conditions including Stevens-Johnson syndrome, bullous pemphigoid, arthralgia, myalgia, pain in extremity, back pain, arthropathy, impaired renal function, acute renal failure.

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION:
Glytec-M 50/500mg (Sitagliptin/Metformin HCl) Tablets are available in pack size of 14's.
Glytec-M 50/1000mg (Sitagliptin/Metformin HCl) Tablets are available in pack size of 14's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
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