Glytec-M XR Tablets

(Sitagliptin USP/Metformin HCl USP)

گلائی ٹیک۔ایم ایکس آر ٹیبلیٹس

(سیٹاگلپٹن یو ایس پی/میٹفورمن ہائیڈروکلورائیڈ یو ایس پی)

WARNING: LACTIC ACIDOSIS

Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, discontinue **Glytec-M XR Tablets** and hospitalize the patient immediately.

COMPOSITION:

Glytec-M XR tablet 50mg/500mg: Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin 50mg
Metformin HCl USP (as Extended Release) 500mg
(As per Innovator's Specifications)

Glytec-M XR tablet 50mg/1000mg: Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin 50mg
Metformin HCl USP (as Extended Release) 1000mg
(As per Innovator's Specifications)

Glytec-M XR tablet 100mg/1000mg: Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP eq. to Sitagliptin 100mg
Metformin HCl USP (as Extended Release) 1000mg
(As per Innovator's Specifications)

DESCRIPTION: Glytec-M XR (Sitagliptin+Metformin HCl) contains two oral antihyperglycemic agents with complementary mechanism of action to improve glycemic control with type 2 diabetes. Sitagliptin is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzymes. Chemically, it is 7-[(3R)-3- amino - 1-oxo -4- (2,4,5 trifluorophenyl) butyl] -5,6,7,8 -tetrahydro -3-(trifluoromethyl) 1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. Its molecular formula is C16H15F6N5O•H3PO4•H2O. Metformin HCl (N,N-dimethylimidodicarbon-imidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. It has a molecular formula of C4H11N5.HCl.

INDICATIONS: Glytec-M XR (Sitagliptin+Metformin HCl) is indicated as: - Initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control. - As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on Metformin HCl or Sitagliptin alone or in patients already being treated with the combination of Sitagliptin and Metformin HCl. - In triple combination with a sulphonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled on their maximal tolerated dose of Metformin HCl and a sulphonylurea. - In triple combination with a peroxisome proliferator-activated receptor gamma (PPARg) agonist (thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of Metformin HCl and a PPARg agonist. - In patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin.

DOSAGE AND ADMINISTRATION: The dosage of **Glytec-M XR** (Sitagliptin+Metformin HCl) should be individualized on the basis of patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100mg Sitagliptin. It should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with Metformin HCl.

As initial therapy: For patients with type 2 diabetes mellitus, whose hyperglycemic is inadequately controlled with diet and exercise alone, the recommended starting dose of **Glytec-M XR** (Sitagliptin+Metformin HCl) is 50mg of Sitagliptin+500mg of Metformin HCl twice daily. Patients may be titrated upto 50mg Sitagliptin+1000mg of Metformin HCl twice daily.

For patients inadequately controlled on Metformin monotherapy: The usual starting dose of **Glytec-M XR** (Sitagliptin+Metformin HCl) should provide Sitagliptin dosed as 50mg twice daily (100mg total daily dose), plus Metformin HCl dose already being taken.

For patients inadequately controlled on Sitagliptin monotherapy: The usual starting dose of **Glytec-M XR** (Sitagliptin+Metformin HCl) is 50mg Sitagliptin+500mg Metformin HCl twice daily. Patients may be titrated up to 50mg Sitagliptin+1000mg Metformin HCl twice daily.

CLINICAL PHARMACOLOGY: Mechanism of Action: Sitagliptin: It is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.
Metformin HCl: Metformin HCl is a biguanide that improves glycemic control in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin HCl decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

PHARMACOKINETICS: The results of a study in healthy subjects demonstrated that the **Glytec-M XR** (Sitagliptin and Metformin HCl extended-release) 50mg/500mg and 100mg/1000mg tablets are bioequivalent to coadministration of corresponding doses of sitagliptin and metformin hydrochloride extended-release. After administration of two **Glytec-M XR** 50mg/1000mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5 respectively.
Absorption: After administration of **Glytec-M XR** tablets with a high-fat breakfast, the AUC for Sitagliptin was not altered. The mean Cmax was decreased by 17%, although the median Tmax was unchanged relative to the fasted state. After administration of **Glytec-M XR** with a high-fat breakfast, the AUC for metformin increased 62%, the Cmax for metformin decreased by 9%, and the median Tmax for metformin occurred 2 hours later relative to the fasted state.
Distribution: Sitagliptin: The mean volume of distribution at steady state following a single 100mg intravenous dose of Sitagliptin to healthy subjects is approximately 198 liters. The fraction of Sitagliptin reversibly bound to plasma proteins is low (38%).
Metformin HCl: Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of Metformin hydrochloride

tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally<1mcg/ml. During controlled clinical trials of Metformin, maximum Metformin plasma levels did not exceed 5mcg/ml, even at maximum doses.
Metabolism: Sitagliptin: Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a [14C] Sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of Sitagliptin was CYP3A4, with contribution from CYP2C8.
Metformin HCl: Intravenous single-dose studies in normal subjects demonstrate that Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or billary excretion. Metabolism studies with extended-release Metformin tablets have not been conducted.
Excretion: Sitagliptin: Following administration of an oral [14 C] 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 t1/2 following a 100mg oral dose of Sitagliptin was approximately 12.4 hours and renal clearance was approximately 350ml/min. Elimination of Sitagliptin occurs primarily via renal excretion and involves active tubular secretion.
Metformin HCl: Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. 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 17.6hours, suggesting that the erythrocyte mass may be a compartment of distribution.

CONTRAINDICATIONS: The combination of Sitagliptin and Metformin HCl is contraindicated in: - Patients with type 1 diabetes. - Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥ 1.5mg/dL (males) ≥ 1.4mg/dL (females), or abnormal creatinine clearance, which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia. - Patients with known hypersensitivity to Sitagliptin, Metformin HCl or anyother component of the product. - Acute or chronic metabolic acidosis, including ketoacidosis, with or without coma. - Children below 18 years of age.

WARNINGS AND PRECAUTIONS:
***Lactic Acidosis**
***Impaired Hepatic Function**
***Assessment of Renal Function**
***Vitamin B_{12} Levels**
Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.
***Alcohol Intake:** Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving **Glytec-M XR.**
***Surgical Procedures:** Use 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.

PREGNANCY AND LACTATION:
Pregnancy: The safety of Sitagliptin+Metformin HCl in pregnant women is not known. So like other antihyperglycemic agents, it is not recommended for use in pregnancy.
Breast-feeding: It is not known whether Sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, Sitagliptin+Metformin HCl should not be administered during nursing.

SIDE EFFECTS: Sitagliptin with Metformin HCl.
Common: Nausea.
Uncommon: Somnolence, diarrhea, upper abdominal pain and blood glucose decreased.
Sitagliptin with Metformin HCl and Sulphonylurea.
Very common: Hypoglycemia.
Common: Constipation.
Sitagliptin with Metformin HCl and a PPAR agonist.
Common: Hypoglycemia, headache, diarrhea,vomiting and peripheral edema.
Sitagliptin with Metformin HCl and insulin.
Very common: Hypoglycemia.
Uncommon: Headache and dry mouth

DRUG INTERACTIONS: Sitagliptin: Digoxin: Sitagliptin has a small effect on plasma digoxin concentrations. No dosage adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when Sitagliptin and digoxin are administered concomitantly.
Metformin HCl: Furosemide: Furosemide increased the Metformin HCl plasma and blood C_{max} by 22%and blood AUC by 15%, without any significant change in Metformin HCl renal clearance.
Nifedipine: Co-administration of nifedipine increased plasma Metformin HCl C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected.
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 HCl by competing for common renal tubular transport systems.

OVERDOSE:
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 obtain an electrocardiogram) and institute supportive therapy as dictated by the patient's clinical status.
Metformin HCl: Incase of Metformin HCl overdose (greater than 50g), hypoglycaemia was reported in approximately 10% of cases. Metfromin HCl is dialyzable with aclearance of up to 170ml/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom Metformin HCl overdosage is suspected.

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

PRESENTATION: **Glytec-M XR** tablet 50mg/500mg, 50mg/1000mg, 100mg/1000mg are available in the pack size of 14's.

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:
NABIQASIM INDUSTRIES (PVT.) LTD.
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