PILGAT-M

(Sitagliptin + Metformin HCl)

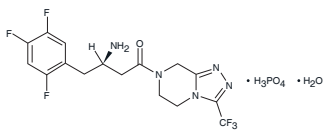
50mg/500mg, 50mg/1000mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION:

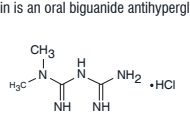
PILGAT-M 50mg/500mg Tablets
Each film-coated tablet contains:
Sitagliptin phosphate U.S.P. eq. to Sitagliptin.....50mg
Metformin HCl U.S.P. 500mg
PILGAT-M 50mg/1000mg Tablets
Each film-coated tablet contains:
Sitagliptin phosphate U.S.P. eq. to Sitagliptin.....50mg
Metformin HCl U.S.P. 1000mg

DRUG DESCRIPTION: Sitagliptin/Metformin HCl tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Sitagliptin and Metformin Hydrochloride.

Sitagliptin: Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.



Metformin: Metformin is an oral biguanide antihyperglycemic agent.



WARNING: LACTIC ACIDOSIS

- Lactic acidosis can occur due to metformin accumulation. The risk increase with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment and acute congestive heart failur.
- 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 Sitagliptin/Metformin HCl and hospitalize the patient immediately.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sitagliptin is a DPP-4 inhibitor, which is believed to exert its action in patients with type 2 diabetes by slowing the inactivation of incretin hormones. 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. These hormones are rapidly inactivated by the enzyme DPP-4. Metformin hydrochloride 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.

PHARMACOKINETICS

Absorption Sitagliptin: The absolute bioavailability of sitagliptin is approximately 87%. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin. Metformin hydrochloride: The absolute bioavailability of a metformin hydrochloride 500mg tablet given under fasting condition is approximately 50-60%. **Metabolism Sitagliptin:** Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. Metformin hydrochloride: 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) nor biliary excretion. **Excretion Sitagliptin:** Following administration of an oral [14C] 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 12.4hours and renal clearance was approximately 350 ml/min.
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. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

INDICATIONS: PILGAT-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.

DOSAGE AND ADMINISTRATION

Recommended Dosing: The dosage of PILGAT-M should be individualized on the basis of the patient's current regimen, effectiveness & tolerability while not exceeding the maximum 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. PILGAT-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 PILGAT-M should be based on the patient's current regimen. PILGAT-M should be given twice daily with meals. The following doses are available: 50 mg sitagliptin/500 mg metformin hydrochloride 50 mg sitagliptin/1000 mg metformin hydrochloride. 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 PILGAT-M is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients treated with an insulin secretagogue or insulin Co-administration of PILGAT-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.

SIDE EFFECTS: This medication may cause lactic acidosis (a build-up of lactic acid in the body, which can be fatal). Lactic acidosis can start slowly and get worse over time. Get emergency medical help if you have even mild symptoms of lactic acidosis, such as: muscle pain or weakness, numb or cold feeling in your arms and legs, trouble breathing, stomach pain, nausea with vomiting, slow or irregular heart rate, dizziness, or feeling very weak or tired. Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling.

PRECAUTIONS: Lactic Acidosis Metformin hydrochloride Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with (Sitagliptin/Metformin HCl) 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.
Use In Specific Populations.

PREGNANCY:

Pregnancy Category B: The safety of PILGAT-M in pregnant women is not known. PILGAT-M should be used during pregnancy only if clearly needed. Nursing Mothers It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PILGAT-M is administered to a nursing woman. Pediatric Use Safety and effectiveness of PILGAT-M in pediatric patients under 18 years have not been established. Geriatric Use Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, PILGAT-M should be used with caution as age increases. **Overdose:** Sitagliptin During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 m/sec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important. There is no experience with doses above 800 mg in clinical studies. Metformin hydrochloride Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. 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. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

CONTRAINDICATIONS: PILGAT-M (Sitagliptin/Metformin HCl) 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 PILGAT-M or sitagliptin (one of the components of PILGAT-M), such as anaphylaxis or angioedema.

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION: PILGAT-M (Sitagliptin/Metformin HCl) 50mg/500mg tablets are available in Alu-Alu blister pack of 2x7's with leaf insert.
PILGAT-M (Sitagliptin/Metformin HCl) 50mg/1000mg tablets are available in Alu-Alu blister pack of 2x7's with leaf insert.

Manufactured for:
DANEEN PHARMA **Daneen Pharma (Pvt.) Ltd.**
27-Sundar Industrial Estate, Sundar Raiwind Road Lahore, Pakistan.
Tel: +92-42-35297781-2, **Email:** info@daneenpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.daneenpharma.com

Manufactured by:
GENIX **Genix Pharma (Pvt.) Ltd.**
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
ISO 9001:2015 ISO 14001:2015 ISO 45001:2018
www.genixpharma.com