Glitamet®

Sitagliptin & Metformin Hydrochloride

COMPOSITION

Glitamet® 50/500 Tablet : Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate and Metformin Hydrochloride 500 mg.
Glitamet® 50/1000 Tablet : Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate and Metformin Hydrochloride 1000 mg.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Oral Antidiabetic Drugs (Antidiabetic Preparations)

Mechanism of action

Glitamet® combines two antihyperglycemic agents 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 is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin 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. 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 by intracellular signaling pathways involving cyclic AMP. 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. The pharmacologic mechanism of action of Metformin is different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and increases peripheral glucose uptake and utilization.

Pharmacokinetics

Sitagliptin:

Absorption:
Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food. Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for Cmax and C24hr (Cmax increased in a greater than dose-proportional manner and C24hr increased in a less than dose proportional manner).

Distribution:
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation:
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine. Following a sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination:
Following administration of an oral sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal t½ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. In vitro, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Metformin:

Absorption:
After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 μg/mL, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution:
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 L.

Biotransformation:
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:
Renal clearance of metformin is >400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Patients treated with an insulin secretagogue or insulin
Co-administration of the combination 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.

Missed Dose:
If a dose of **Glitamet®** is missed, it should be taken as soon as the patient remembers. If he/she does not remember until it is time for the next dose, the missed dose should be skipped and returned to the regular schedule. A double dose of **Glitamet®** should not be taken at the same time.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not use the combination of Sitagliptin & Metformin in patients with hepatic disease.
• Before initiating the combination and at least annually thereafter, assess renal function and verify as normal.
• May need to discontinue the combination and temporarily use insulin during periods of stress and decreased intake of fluids and food as may occur with fever, trauma, infection or surgery.

EFFECTS ON ABILITY TO DRIVE AND USE OF MACHINES

Glitamet® has no or negligible influence on the ability to drive and use of machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with Sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when **Glitamet®** is used in combination with a sulphonyl urea or with insulin.

UNDESIRABLE EFFECTS

The most common (>5%) adverse reactions due to initiation of Metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

OVERDOSE

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. 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 haemodialysis. In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis 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.

CONTRAINDICATIONS

Combination (Sitagliptin/Metformin Hydrochloride) 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].
• Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
• History of a serious hypersensitivity reaction to the combination or sitagliptin, such as anaphylaxis or angioedema.

DRUG INTERACTION

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.
Co-administration of Digoxin and Sitagliptin may slightly increase the mean peak drug concentration of Digoxin. But no dosage adjustment of digoxin or Sitagliptin is recommended.

USE IN SPECIAL POPULATION

Pregnancy & Lactation:
Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women with the combination of Metformin/Sitagliptin or its individual components; therefore, the safety of the combination in pregnant women is not known. The combination of Sitagliptin & Metformin 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 this combination is administered to a nursing woman.

Geriatric use:
Because Sitagliptin and Metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, combination of Sitagliptin and Metformin 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.

Pediatric use
Safety and effectiveness of Sitagliptin / Metformin in pediatric patients under 18 years of age have not been established.

STORAGE

Store below 30°C in a dry place. Keep away from light. Keep out of reach of children.

HOW SUPPLIED

Glitamet® 50/500 Tablet : Each box contains 10/30/60 tablets in blister pack.
Glitamet® 50/1000 Tablet : Each box contains 10/30/60 tablets in blister pack.

SQUARE