Sitamet®

Metformin Hydrochloride BP + Sitagliptin

Composition:
Each tablet contains two oral antihyperglycemic drugs: Metformin Hydrochloride BP 500mg & Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate.

Mechanism of action:
Sitamet 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 DPP-4 inhibitor, which is believed to exert its actions 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. 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. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Metformin is an antihyperglycemic 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 antihyperglycemic agents. 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 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.

Indications:
1. As mono-therapy, as an adjunct to diet to lower blood glucose in patients with NIDDM whose hyperglycemia cannot be satisfactorily managed on diet alone.
2. As adjunct therapy for IDDM in combination with insulin.

Dosage & Administration:
Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2,550 mg (Metformin). Initially 500 mg (Metformin) twice daily or 850 mg (Metformin) daily with meals increasing gradually if necessary to maximum 3 gm daily. Reduce to maintenance, usually 500 mg (Metformin) thrice or 850 mg (Metformin) twice daily.

Pharmacodynamics:
In patients with type 2 diabetes, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes.

Absorption:
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.

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).
The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. 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 < 1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

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

Excretion:
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 t½ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and 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, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. 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 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Side effects:
Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment. Adverse reactions occurring in 3% of patients include diarrhoea, nausea, vomiting, abdominal bloating, flatulence, anorexia, unpleasant metallic taste.
Drug interactions:

Contraindications
1. Severe renal insufficiency
2. Acute complications (severe infections, major operations and trauma)
3. Liver damage
4. Alcoholism
5. Deficiencies of Vitamin B12, folic acid and iron.
6. Severe cardiovascular or respiratory disease
7. Diabetes with significant late complications (nephropathy, retinopathy)

High Risk Group
Neonates: This combination is not used in this age group
Children: This combination is not recommended in children
Adult: Caution is advised in elderly patients because of the reduced renal function with increasing age. Frequent monitoring of serum creatinine and dose reduction is recommended in this group.
Pregnant women: The drug has been used in pregnant women without any particular problems. Nevertheless, pregnancy is generally regarded as a contraindication and insulin should be used in all pregnant diabetic women.
Lactating mother: Metformin may enter breast milk and is best to avoided in nursing mothers

Storage: Store in a cool and dry place, away from direct light and children.

Presentation: Each box contains 1x10 tablets in blister pack.

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Manufactured by:
RENATA LIMITED
Mirpur, Dhaka, Bangladesh