TAGLIMET

SITAGLIPTIN PHOSPHATE USP + METFORMIN HYDROCLORIDE BP

Compositions:
Taglimet 50/500 Tablet: Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate (Monohydrate) USP and Metformin Hydrochloride BP 500 mg. Taglimet 50/1000 Tablet: Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate (Monohydrate) USP and Metformin Hydro chloride BP 1000 mg.

Pharmacology:
Taglimet (Sitagliptin/Metformin HCI combination) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes, sitagliptin and metformin hydrochloride. Sitagliptin Phosphate is an orally-active potent and highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, Sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). 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. 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 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 sulfonytureas. metformin does not produce hypoglycemia in either patient with type 2 diabetes or normal subjects 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.

Dosage And Administration:
The dosage of Taglimet should be individualized on the basis of the patient's current regimen, effectiveness and tolerability while not exceed ing the maximum recommended 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. Taglimet 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 Taglimet should be based on the patient's current regimen. 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 recom mended 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 Taglimet is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Co-ad ministration of Taglimet 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. No studies have been performed specifically examining the safety and efficacy of Taglimet in patients previously treated with other oral antihypergtycemic agents and switched to Taglimet. Any change in therapy of type

2 diabetes should be undertaken with care and appropriate monitoring as changes in grycemic control can occur.

Contraindications:
Sitagliptin/Metformin HCI combination is contraindicated in patients with: Renal disease or renal dysfunction, e.g., as suggested by serurn creatinine levels 0.5 mg/dL [males], Z1.4 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 Sitaglipt in/Metformin HCI combination or Sitagliptin such as anaphylaxis or angioedema. This combination drugs should be temporarily discontinued in patients undergoing radiologic studies involving intravascular adminis tration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Warning And Precaution:
Lactic acidosis is a rare but serious, metabolic complication that can occur due to metformin accumulation during treatment with Sitagliptin Metformin HCI combination; 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. There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin/Metformin HCI combination. After initiation of Sitagliptin/Metformin HCI combination, patients should be observed carefully for signs and symptoms of pancreatitis, if pancreatitis is suspected, Sitagliptin/Metformin HCI combination should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancre atitis while using Sitagliptin/Metformin HCI combination. Since impaired hepatic function has been associated with some cases of lactic acidosis, Sitagliptin/Metformin HCI combination should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metforrnin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive Sitagliptin/Metformin HCI combination. In the elderly, Sitaglipt in/Metformin HCI combination should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging can be associated with reduced renal function.

Side Effects:
The most common adverse reactions reported in >5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection and headache. Nasopharyngitis was the only adverse reaction reported in 5% of patients treated with sitagliptin monotherapy. Hypogly cemia was also reported more commonly in patients treated with the combination of Sitagliptin and sulfonylurea, with or without Metformin, than in patients given the combination of placebo and sulfonylurea, with or without Metformin. The most common established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia and headache.

Use in Pregnancy and Lactation:
Neomycin Sulphate in pregnant women. Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. However, neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity. Thus use of Betamethasone Valerate & Neomycin Sulphate is not recommended in pregnancy

& lactation.

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. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 1Oday. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin/Metformin is recommended. 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 HCI combination the patient should be closely observed to maintain adequate glycemic control.

Overdosage:
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 as indicated by the patient's clinical status. Sitagliptin is modestly dialyzable. In clinical studies, 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 dialyzable by peritoneal dialysis. 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. Metformin is dialyzable with a clearance of up to 170 ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin over dosage is suspected.

Storage:
Store in a cool (below 30°C) and dry place. Keep out of the reach of the children.

Packing:
Taglimet 50/500 Tablet: Each box contains 3 x 10 tablets in blister packs. Taglimet 50/1000 Tablet: Each box contains 3 x 10 tablets in blister packs.

Manufactured By:
The IBN SINA Pharmaceutical Industry PLC.
Shafipur, Gazipur, Bangladesh.