STEGLIP-M

(Sitagliptin + Metformin HCl)

Tablet

COMPOSITION:

STEGLIP-M -50/500 Tablet.

Each film coated tablet contains:

Sitagliptin(as phosphate monohydiate) U.S.P. .....50mg.

Metformin HCl BP ..... 500mg.

Innovator's Specifications:

STEGLIP-M 50/1000 Tablet

Each film coated tablet contains:

Sitagliptin(as phosphate monohydiate) U.S.P. ..... 50mg.

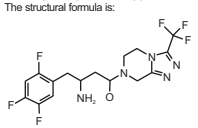
Metformin HCl BP ..... 1000mg.

Product Specs: As per innovator's specifcations.

DESCRIPTION:

STEGLIP-M (sitagliptin and metformin HCl) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Sitagliptin and metformin hydrochloride.

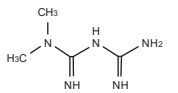
Sitagliptin: Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in **STEGLIP-M** tablets in the form of sitagliptin phosphate monohydrate. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1.1) monohydrate with an empirical formula of C16H15F6N5O+H3PO4+H2O and a molecular weight of 523.32. The structural formula is:



.$H_3PO_4.H_2O$

Metformin hydrochloride:

Metformin hydrochloride is a compound with a molecular formula of $C_4H_{11}N_5$.HCl and a molecular weight of 165.63. The structural formula is as shown:



.HCl

CLINICAL PHARMACOLOGY:

Mecganism of action:

STEGLIP-M Tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus; sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which exerts 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 pgysiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release form pancreatic beta cells by intracellular signaling pathways involving cyclic AMP.GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucoseproduction, By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decrease 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 hydrochloride: Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, 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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or healthy subjects except in certain circumstances and does not cause hyperinsulinemia. With metfomin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics:

Absorption:

Sitagliptin: After oral administration of a 100mg dose to healthy subjects, sitagliptin is rapadily absorbed with peak plasma concentrations 9medium Tmax) occuring 1 to 4 hours postdose. the absolute bioavailbility of sitagliptin is approximately 87%. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetins of sitagliptin.

Metformin hydrochloride: The absolute bioavailability of Metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax0, a25% lower area under the plasma concentration versus time curve 9AUC), and 35-minute prolongation of tme to peak plasma concentration 9Tmax0 following adminstration of a single 850mg tablet of Metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:

Sitagliptin;

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

Metformin hydrochloride: Distribution volume of immediate-release metformin hydrochloride tablets 850mg averaged 654+358 L.Metformin is negligibly bound to plasma proteins. Steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally<1 mcg/mL.

Elimination:

Sitagliptin: Approximately 79% of sitagliptin is excreted unchanged in the urine whit metabolism being a minor pathway of elimination. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was approximately12.4 hours and renal clearance was approximately 350mL/min.

Metformin hydrochloride: Following oral administration, approximately 90% of the absorbed drug is eleminated via the renal route within the first 24 hours, with 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.

Metabolism:

Sitagliptin: Following a [14C] sitagliptin oral dose, approximately 16% of the radioactivity was excreated as metabolites of sitagliptin. Six metabolities 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 levels are not expected to contribute to the plasma DPP-4 inhibitory activity 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) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion:

Sitagliptin: Following administration of an oral[14C] sitagliptin dose to healthy subjects, approximately 100% of the administrated radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. Elimination of sitagliptin occures primarily via renal excretion and involves active tubular secretion.

Metaformin hydrochloride:Elimination of metformin occures primarily via renal excretion. Renal clearence is approximately 3.5 times greater than creatinine clearence, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations:

Patients with renal impairment:

Sitagliptin: An approximately 2-fold increase in the plasma AUC of sitagliptin obsurved in patients with moderate renal impairment with eGFR of 30 to less than 46 mL/min/1.73m2 and an approximately 4-fold increase observed in in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects.

Metformin hydrochloride: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearence is decreased.

Patients with hepatic impairment:

Sitagliptin: In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13% respectively compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score>9)

Metaformin Hydrochloride:

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of age, body mass index(bmi),gender and race:

Sitagliptin: Based on a population pharmacokinetic analysis of BMI,gender and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin.

Metaformin hydrochloride:Pharmacokinetic studies of metformin in healthy elderly subjects sugget that total plasma clearance of metformin is decreased, the half-life is prolonged and C_{max} is increased, compared to healthy young subject .

Pediatric patients:

Sitagliptin: Studies characterizing the pharmacokinitics of sitagliptin in pediatric patients have not been performed.

INDICATIONS AND USAGE:

STEGLIP-M is indicated as an adjunct to diet and excercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

Important limitations of use:

- **STEGLIP-M** should not be used in patients of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- It is unknown whether patients with a history of pancreatitis are at increased risk for the developmentof pancreatitis while using STEGLIP-M.

DOSAGE AND ADMINISTRATION:

Give twice daily with meals with gradual dose escalation to reduce the gastrointestinal effects due to metformin.

- Individualize the starting dose of **STEGLIP-M** based on the patient's current regimen.
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR)

DOSE MODIFICATION RECCOMENDATIONS.

Recommendations for use in renal impairment: Assess renal function prior to initiation of STEGLIP-M and periodically thereafter. **STEGLIP-M** is contrainidicated in patients with an estimated glomerular filtration rate (eGFR) below 30mL/mim/1.73m^2 . **STEGLIP-M** is not recomended in patients with an eGFR between 30and less than 45 mL/min/1.73m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination **STEGLIP-M** product

Discontinuation for iodinated contrast imaging procedures : Discontinue **STEGLIP-M** at the time of, or prior to an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73m^2, in patients with a history of lever disease, alcohalism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast. Reevaluate eGFR 48 hours after the imaging procedure, restart **STEGLIP-M** if renal function is stable.

CONTRAINDICATIONS:

STEGLIP-M (sitagliptin and metformin Hcl) is contraindicated in patients with:

- Severe renal impairment (eGFR below 30mL/min/1.73m^2).
- Hypersensitivity to metformin hydrochloride/
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insuline.
- History of a serious hypersnsitivity reaction to **STEGLIP-M** or sitagliptin (one of the components of **STEGLIP-M)**, such as anaphylaxis or angioedema.

WARNINGS AND PRECAUTIONS:

- ***Lactic acidosis:*** Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension and resistance bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence and abdominal pain. If lactic acidosis is suspected discontinue **STEGLIP-M** and insitute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.
- Acute pancreatitis, including fatal and non-fatal hemmorhagic or necrotizing pancreatitis. If pancreatitis is suspected promptly discontinue **STEGLIP-M.**
- Heart failure has been observed with two other members of DPP-4 inhibitor class. Consider risks and benefits of **STEGLIP-M** in patients who have known risk factor of heart failure. Monitor patients for signs and symptoms.
- There have been post marketing reports of acute renal failure, sometimes requiring dialysis. Before initiating **STEGLIP-M** and at least annually, thereafter access renal function.
- ***Vitamin B_{12} deficiency:*** Metformin may lower Vitamin B12 levels. Measure hematologocal parameters annually.
- When used with an insuline secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.
- There have been post marketing reports of serious alergic and hypersensitivity reactions in patients treated with sitagliptin, such as anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases promptly stop **STEGLIP-M** access for other potential causes, and institute appropriate monitoring and treatment and initiate alternative treatment for diabates.
- Severe and disabling arthelgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.
- There have been postmarketing reports to bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blistors and erosions. If bullous pemphigoid is suspected, disconyinue **STEGLIP-M.**
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with **STEGLIP-M.**

DRUG INTERACTIONS:

Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. Drugs that reduce metformin clearance (such as renolazine, vanditanib, dolutegravir and cemetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use.

Alcohol; Can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. Insulin secretagogues or insulin: Co- administration of **STEGLIP-M** with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin reduce the risk of hypoglycemia.

Use of metformin with other drugs: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, cortocosteroids, phenothiazines, thyroid products, oral contraceptives, phenytoin, nicotinic acid, sympathominetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to a patienr receiving **STEGLIP-M** the patient should be closely observed to maintain adequate glycemic control.

Digoxin: There was a slight increase in the area under the curve (AUC 11%) and mean peak drug concentration (Cmax 18%) of digoxin with the coadministration of 100mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or **STEGLIP-M** is recommended.

USE IN SPECIFIC POPULATIONS:

Pregnancy: The limited available data with Sitagliptin / Metformin Hydrochloride preparation use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage

Lactation: There is no information regarding the presence of **STEGLIP-M** in human milk, the effects on the breastfed infants or the effects on milk production. The developmental and health benefits of breastfeeding should be cosidered along with the mother's clinical need for **STEGLIP-M** and any potential adverse effects on the breastfeed infant from **STEGLIP-M** or from the underlying maternal condition.

Pediatric use: Safety and effectiveness of **STEGLIP-M** in pediatric patients under 18 years have not been established.

Geriatricuse: Assess renal function more frequently.

Patints with renal impairment:

STEGLIP-M: The dose of the sitagliptin component should be limited to 50mg once daily eGFR falls below 45mL/min/1.73m^2.

STEGLIP-M is contraindicated in severeal renal impairment, patients with an eGFR below 30mL/min/1.73m^2.

Patients with hepatic impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. **STEGLIP-M** is not recommended in patients with hepatic impairment.

ADVERSE REACTIONS:

- 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 rispiratory tract infection and headache. Adverse reactions reported in ≥ 5% of patients treated with sitagliptin in combination with sulfonylurea and metformin and more commonly than in patients treated with placebo in combination with sulfonylurea and metformin were hypoglycemia and headache.
- Hypoglycemia was the only adverse reaction reported in ≥ 5% of patients treated with sitagliptin in combination with insulin and metformin and more commonly than in patients treated with placebo in combination with nsulin and metformin.

Post marketing experience:

Additional adverse reactions have been identified during post marketing use of combination, sitagliptin or metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a casual relationship to drug exposure. Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions including Stevens-Johnson syndrome, upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis, worsening renal function, including acute renal faliure (sometimes requiring dialysis), severe and disabling arthralgia, bullous pemphigoid, constipation, vomiting, headache, myalgia, pain in extremity, back pain, pruritus, mouth ulceration, stomatitis, cholestatic, hepatocellular and mixed hepatocellular liver injury.

OVERDOSAGE:

Sitagliptin: In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material fron the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram) and institute supportive therapy as indicated by the patient's clinical status. Prolonged hemodialysis may be considered if clinically appropriate. it is not known if sitagliptin is dialyzable by peritoneal dialysis.

Metformin hydrochloride; 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 overdosage is suspected.

INSTRUCTIONS:

-Store below 30°C.
-Protect from heat, sunlight & moisture.
-Keep out of the reach of children.
-To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Steglip-M 50/500 Tablet : Pack of 3x10's tablets
Steglip-M 50/1000 Tablet : Pack of 2x7's tablets
Steglip-M 50/500 Tablet : Pack of 2x7's tablets

Manufactured by :

Pharmedic Laboratories (Pvt) Limited.

16 Km. Multan Road, Lahore - Pakistan