Formet-L

Metformin Hydrochloride & Linagliptin

COMPOSITION

Formet-L 500/2.5 Tablet: Each film coated tablet contains Metformin Hydrochloride BP 500 mg & Linagliptin INN 2.5 mg.

PHARMACOLOGY

Formet-L combines 2 antihyperglycemic agents (combination of Linagliptin, a DPP-4 inhibitor & Metformin Hydrochloride, a member of the biguanide class) with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus.

Linagliptin: Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, Linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin: Metformin lowers both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglyceamia or increased weight gain. Metformin may exert its glucose-lowering effect via four mechanisms:

- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization;
- by delaying intestinal glucose absorption;
- stimulate intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of glucose transporters (GLUT-1 & GLUT-4)

PHARMACOKINETICS

Absorption

Linagliptin: The absolute bioavailability of Linagliptin is approximately 30%. Following oral administration, plasma concentrations of Linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of Linagliptin to DPP-4. The effective half-life for accumulation of Linagliptin, as determined from oral administration of multiple doses of Linagliptin 5 mg, is approximately 12 hours. The pharmacokinetics of Linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin: The absolute bioavailability of a Metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of Metformin 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.

Distribution

Linagliptin: The mean apparent volume of distribution at steady state following a single intravenous dose of Linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that Linagliptin extensively distributes to the tissues.

Metformin: The apparent volume of distribution (V/F) of Metformin following single oral doses of immediate-release Metformin Hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs. which are more than 90% protein bound.

Metabolism

Linagliptin: Following oral administration, the majority (about 90%) of Linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed Linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to Linagliptin.

Metformin: 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

Linagliptin: Following administration of an oral [14-C] Linagliptin dose to healthy subjects. approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 ml/min.

Metformin: 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.

INDICATIONS

Formet-L is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Metformin & Linagliptin is appropriate. Combination of Metformin & Linagliptin is not recommended for treatment of type 1 diabetes or diabetic ketoacidosis and has not been studied in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION

Recommended starting dose*

- **Patients not currently treated with Metformin:** Initiate treatment with **Formet-L** tablet twice daily.
- **Patients already treated with Metformin:** If patient is taking Metformin 500 mg tablet twice daily, then give him/her **Formet-L 500/2.5** tablet twice daily.

CONTRAINDICATIONS

This combination of Metformin & Linagliptin is contraindicated in peke-:s with renal impairment (e.g., serum creatinine ≥ 1.5 mg/dl for men, ≥ 1.4 mg/dl for women. or abnormal creatinine clearance). which may also result from conditio such as cardiovascular collapse (shock), acute myocardial infarction, and septicemea. This combination is also contraindicated in case of acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin. In case of a history of hypersensitivity reaction to Linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity it is also contraindicated.Contraindicated in case of hypersensitivity to Metformin.

ADVERSE REACTIONS

The most common side effects of this combination of Metformin & Linagliptin are weakness or tiredness, unusual muscle pain, breathing in trouble, nausea, vomiting, diarrhea, dizziness. Adverse reactions reported in 75% of patients treated with Metformin & Linagliptin combination and more commonly than in patients treated with placebo are nasopharyngitis and diarrhea. Hypoglycemia was more commonly reported in patients treated with the combination of Metformin & Linagliptin and Sulfonylureas compared with those treated with the combination of Sulfonylureas and Metformin.

WARNINGS AND PRECAUTIONS

Lactic acidosis: Warn against excessive alcohol use. Metformin & Linagliptin combination is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.

Hypoglycemia: When used with an insulin secretagogue (e.g., sulfonylurea (SU)) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Linagliptin (one of the components of Metformin & Linagliptin combination) including anaphylaxis. angioedema, and exfoliative skin conditions. In such cases, promptly discontinue Metformin & Linagliptin combination, assess for other potential causes, and institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.

Vitamin B12 deficiency: Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.

Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.

Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with Linagliptin & Metformin combination or any other antidiabetic drug. If pancreatitis is suspected. promptly discontinue Metformin & Linagliptin combination.

DRUG INTERACTIONS

Drug Interactions with Metformin

Cationic Drugs: Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine. ranitidine, triamterene, trimethoprim, or vancomycin) that are excreted by renal secretion theoretically have the potential for interaction with Metformin by competing for common renal tubular transport systems. Although such interactions rermain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of Metformin & Linagliptin combination and the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g. zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with Metformin & Linagliptin combination, as the risk of lactic acidosis may increase.

Drug Interactions with Linagliptin

Inducers of P-glycoprotein and CYP3A4 Enzymes: Rifampin decreased Linagliptin exposure. suggesting that the efficacy of Linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As Metformin & Linagliptin combination is a fixed-dose combination of Metformin & Linagliptin, use of alternative treatments (not containing Linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category B. Metformin & Linagliptin combination tablets should be used during pregnancy only if clearly needed.

Nursing mothers: Caution should be exercised when Metformin & Linagliptin combination is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Metformin & Linagliptin combination in pediatric patients under 18 years of age have not been established.

Geriatric Use: Linagliptin is minimally excreted by the kidney; however, Metformin is substantially excreted by the kidney. Considering that aging can be associated with reduced renal function, Metformin & Linagliptin combination should be used with caution as age increases.

Renal Impairment: Studies characterizing the pharmacokinetics of Metformin & Linagliptin after administration of Metformin & Linagliptin combination in renally impaired patients have not been performed.

Hepatic Impairment: Studies characterizing the pharmacokinetics of Metformin & Linagliptin after administration of Metformin & Linagliptin combination in hepatically impaired patients have not been performed. However, use of Metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore. use of Metformin & Linagliptin combination is not recommended in patients with hepatic impairment.

STORAGE

Store at 30^{O}C and dry place, protect from light. Keep out of the reach of children.

COMMERCIAL PACK

Formet-L 500/2.5 Tablet: Each box contains 30 tablets in alu-alu blister pack.

Manufactured by

BIOPHARMA
LIMITED
A-116, BSCIC Industrial Estate
TONGI, GAZIPUR, BANGLADESH

For further query on the use of this medicine, consult to a registered Doctor or Pharmacist.