LINA-MET®

(Linagliptin + Metformin HCl)

Tablet

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COMPOSITION:

LINA-MET 2.5/500 mg Tablet:

Each film coated tablet contains:

Linagliptin ..... 2.5 mg.

Metformin HCl ..... 500 mg.

Product Specs.: Innovator

LINA-MET 2.5/850 mg Tablet:

Each film coated tablet contains:

Linagliptin ..... 2.5 mg.

Metformin HCl ..... 850 mg.

Product Specs.: Innovator

LINA-MET 2.5/1000 mg Tablet:

Each film coated tablet contains:

Linagliptin ..... 2.5 mg.

Metformin HCl ..... 1000 mg.

Product Specs.: Innovator

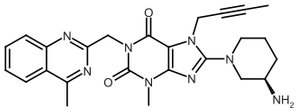
WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- Metformin-associated lactic acidosis has resulted in death, hypothermia, hypotension, and resistant bradyarrhythmia's. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.
- Risk factors include renal impairment, concomitant use of certain drugs, age ⩾ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information.
- If lactic acidosis is suspected, discontinue Linagliptin / Metformin HCl and institute general supportive measures in a hospital setting. Prompt haemodialysis is recommended

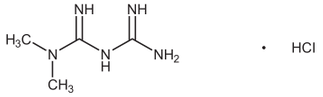
DESCRIPTION:

Linagliptin: Linagliptin is an inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- The molecular formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol.

Metformin HCl: Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63 g/mol. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



• HCl

CLINICAL PHARMACOLOGY:

Mechanism of Action: Linagliptin / Metformin HCl contains: linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a biguanide.

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 HCl: Metformin is an antihyperglycemic agent which improves glucose tolerance 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Pharmacodynamics:

Linagliptin: Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis.

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. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Metformin HCl: The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%.

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. Plasma protein binding of linagliptin is concentration-dependent decreasing from about 99% at 1 nmol/L to 75% to 89% at ⩾30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metformin HCl: 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. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination:

Linagliptin: Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metformin HCl: Metformin has 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.

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 HCl: Metformin does not undergo hepatic metabolism (no metabolites have been identified in humans), nor biliary excretion.

Excretion:

Linagliptin: Following administration of an oral [14C] 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.

Metformin HCl: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

INDICATIONS AND USAGE:

Linagliptin / Metformin HCl is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Limitations of use Linagliptin / Metformin HCl should not be used in patients with type 1 diabetes.

DOSAGE AND ADMINISTRATION:

Recommended Dosing The dosage of Linagliptin / Metformin HCl should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride (HCl) twice daily. Linagliptin / Metformin HCl should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use.

Recommended starting dose:

- In patients currently not treated with metformin HCl, initiate treatment with 2.5 mg linagliptin/500 mg metformin HCl twice daily
- In patients already treated with metformin HCl, start with 2.5 mg linagliptin and the current dose of metformin HCl taken at each of the two daily meals (e.g., a patient on metformin HCl 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin HCl twice daily with meals)
- Patients already treated with linagliptin and metformin HCl individual components may be switched to Linagliptin / Metformin HCl containing the same doses of each component

Recommended dosing in renal impairment:

Assess renal function prior to initiation of Linagliptin / Metformin HCl and periodically thereafter.

Linagliptin / Metformin HCl is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m².

Initiation of Linagliptin / Metformin HCl in patients with an eGFR between 30-45 mL/min/1.73 m² is not recommended.

In patients taking Linagliptin / Metformin HCl whose eGFR later falls below 45 mL/min/1.73 m², assess benefit/risk of continuing therapy.

Discontinue Linagliptin / Metformin HCl if the patient's eGFR later falls below 30 mL/min/1.73 m².

Discontinuation for iodinated contrast imaging procedures:

Discontinue Linagliptin / Metformin HCl at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Linagliptin / Metformin HCl if renal function is stable.

CONTRAINDICATIONS:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²)
- Acute or chronic metabolic acidosis, including diabetic
- Hypersensitivity to linagliptin, metformin, or any of the excipients in Linagliptin / Metformin HCl, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred with

ADVERSE REACTIONS:

- Lactic Acidosis
- Pancreatitis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Hypersensitivity Reactions
- Vitamin B_{12} Deficiency
- Severe and Disabling Arthralgia
- Bullous Pemphigoid
- Heart Failure

WARNINGS AND PRECAUTIONS:

- *Lactic acidosis:* **See boxed warning**
- *Pancreatitis:* There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue Linagliptin / Metformin HCl
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating Linagliptin / Metformin HCl
- *Hypersensitivity reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, and exfoliative skin conditions) have occurred with Linagliptin / Metformin HCl. If hypersensitivity reactions occur discontinue Linagliptin / Metformin HCl, treat promptly, and monitor until signs and symptoms resolve
- *Vitamin B_{12} deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities
- *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
- *Bullous pemphigoid:* There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue Linagliptin / Metformin HCl
- *Heart failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of Linagliptin / Metformin HCl in patients who have known risk factors for heart failure. Monitor for signs and symptoms

DRUG INTERACTIONS:

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) 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
- Strong P-glycoprotein/CYP3A4 inducer: Efficacy may be reduced when administered in combination (e.g., rifampin). Use of alternative treatments is strongly recommended

USE IN SPECIFIC POPULATIONS:

Pregnancy: The limited data with Linagliptin / Metformin HCl and linagliptin use in pregnant women are not sufficient to inform a Linagliptin / Metformin HCl associated or linagliptin-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Lactation: There is limited information regarding the presence of Linagliptin / Metformin HCl or its components (linagliptin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production.

Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Linagliptin / Metformin HCl and any potential adverse effects on the breastfed child from Linagliptin / Metformin HCl or from the underlying maternal condition.

Females and males of reproductive potential: Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Paediatric use: Safety and effectiveness of Linagliptin / Metformin HCl have not been established in paediatric patients.

Geriatric use: Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal impairment: Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Linagliptin / Metformin HCl is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m².

Hepatic impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Linagliptin / Metformin HCl is not recommended in patients with hepatic impairment.

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:

LINA-MET 2.5/500 mg Tablet	:	Pack of 2 x 7 tablets.
LINA-MET 2.5/850 mg Tablet	:	Pack of 2 x 7 tablets.
LINA-MET 2.5/1000 mg Tablet	:	Pack of 2 x 7 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

گرمی، دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.