LINAUR™ -M 500/1000

tablets

1. Generic Name: Linagliptin and Metformin tablets

2. Qualitative and Quantitative composition:

Each film coated tablet contains:

Linagliptin..... 2.5 mg

Metformin Hydrochloride IP ..... 500 mg

Excipients ..... q.s.

Colours: Ferric oxide Yellow & Titanium Dioxide IP

Each film coated tablet contains:

Linagliptin..... 2.5 mg

Metformin Hydrochloride IP ..... 1000 mg

Excipients..... q.s.

Colours: Ferric oxide Red & Titanium Dioxide IP

3. Dosage form and strength:

Dosage form: Tablet is available in oral dosage form.

Strength: 2.5 mg linagliptin/500 mg metformin hydrochloride

2.5 mg linagliptin/1000 mg metformin hydrochloride

4. Clinical particulars

4.1. Therapeutic indication

LINAUR-M-500/1000 is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate

4.2. Posology and method of administration

- The recommended dose of LINAUR-M-500/1000 is twice daily or as directed by the Physician.
- LINAUR-M-500/1000 give twice daily with meals, with gradual dose escalation to reduce the gastrointestinal effects due to metformin
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR)

  Do not use in patients with eGFR below 30 mL/min/1.73 m^2

Initiation is not recommended in patients with eGFR between 30 -45 mL/min/1.73 m^2

Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m^2

Discontinue if eGFR falls below 30 mL/min/1.73 m^2)

Method of administration: For oral use.

4.3. Contraindication

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2)
- Metabolic acidosis, including diabetic ketoacidosis
- History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity
- Hypersensitivity to metformin

4.4. Special warnings and precautions for use:

- Lactic acidosis
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue LINAUR-M.
- 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 LINAUR-M) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue LINAUR-M, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.
- Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} 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.
- Bullous Pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue LINAUR-M.
- Macrovascular outcomes: No conclusive evidence of macrovascular risk reduction with LINAUR-M or any other antidiabetic drug

4.5. 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.

4.6 Use in special population

- **Pediatric:** Safety and effectiveness of LINAUR- M in pediatric patients have not been established
- **Geriatric:** Assess renal function more frequently.
- **Hepatic impairment:** Avoid use in patients with hepatic impairment. Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis.
- **Renal failure:** Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. LINAUR- M is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2
- **Pregnancy and lactation:** Pregnancy Category B. There are no adequate or well-controlled studies in pregnant women.

4.7. Effects on ability to drive and use machine.

Data not available hence not advisable.

4.8. Undesirable effects:

Linagliptin

Adverse Reactions Reported in Patients Treated with Linagliptin + Metformin and Greater than Placebo in Placebo-Controlled Clinical Studies of are Nasopharyngitis, Diarrhea.

Other adverse reactions reported in clinical studies with treatment of linagliptin + metformin were hypersensitivity (e.g., urticaria, angioedema, or bronchial hyperreactivity), cough, decreased appetite, nausea, vomiting, pruritus, pancreatitis, urinary tract infection, hypertriglyceridemia

Metformin

- The most common adverse reactions due to initiation of metformin are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia)
- hypogycemia

4.9. Overdose

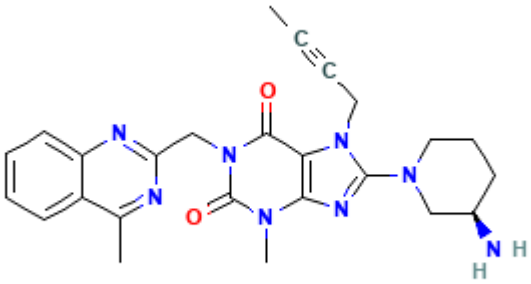
Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

LINAUR-M tablets contain, Linagliptin and Metformin Hydrochloride as the active ingredient, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Linagliptin is described chemically as 8-[(3*R*)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]purine-2,6-dione

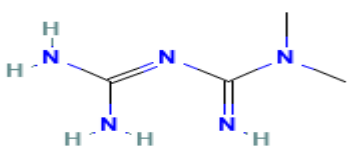
The empirical formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.5 g/mol. The structural formula is:



Metformin Hydrochloride

- Metformin hydrochloride (3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ and a molecular weight of 165.62 g/mol.

  The structural formula is:



5.1. Mechanism of action

LINAUR-M combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

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 is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, 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 SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) 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.

5.2. Pharmacodynamic properties

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. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.

5.3. Pharmacokinetic properties

The results of a bioequivalence study in healthy subjects demonstrated that JENTADUETO (linagliptin/metformin hydrochloride) 2.5 mg/500 mg and 2.5 mg/1000 mg combination tablets are bioequivalent to coadministration

of corresponding doses of linagliptin and metformin as individual tablets. Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg fixed-dose combination with food resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC; however, mean peak serum concentration of metformin was decreased by 18% when administered with food. A delayed time-to-peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant.

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 Cmax 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 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. 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 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. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 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

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 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. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology: Not required.

7. Description

Already mentioned and covered in the above points.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life: 24 months

8.3 Packaging Information

10 Tablets per strip.

8.4 Storage and handling instructions

Store protected from light and moisture, at a temperature not exceeding 30◦C. Keep all medicines out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you. Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor, pharmacist or nurse.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

9.1 Adverse reactions: Refer part 4.8.

9.2 Drug Interactions: Refer part 4.5.

9.3 Dosage: Refer part 4.2.

9.4 Storage: Refer part 8.4.

9.5 Risk factors: Refer part 4.4.

9.6 Self-monitoring information: NA

9.7 Information on when to contact a health care provider or seek emergency help.

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications: Refer part 4.3.

10. Details of manufacturer:

SYNOKEM LIFESCIENCES PVT.LTD

Plot No. 11, Sector 4, IIE SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand.

11. Details of permission or license number with date: 10/UA/2022

12. Date of revision: March 2024