LINAUR™

tablets 5mg

1. Generic Name: Linagliptin

2. Qualitative and Quantitative composition:

Each Film coated tablet contains:

Linagliptin ..... 5 mg

Excipients..... q.s.

Colours: Ferric oxide Red &

Titanium Dioxide IP

3. Dosage form and strength:

Dosage form: Tablets is available in oral dosage form.

Strength: Available in 5mg

4. Clinical particulars

4.1. Therapeutic indication

LINAUR is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

4.2. Posology and method of administration

The recommended dose of LINAUR is 5 mg once daily.

LINAUR tablets can be taken with or without food.

Method of administration: For oral use.

4.3. Contraindication

LINAUR is contraindicated in patients with a history of a hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity

4.4. Special warnings and precautions for use:

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of LINAUR in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. The use of LINAUR in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with LINAUR .

4.5. Drug interactions:

Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure suggesting that the efficacy of LINAUR may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

4.6 Use in special population

- **Pediatric:** Safety and effectiveness of LINAUR in pediatric patients have not been established
- **Geriatric:** No dosage adjustment of lansoprazole is necessary in geriatric patients. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.
- **Hepatic impairment:** No dose adjustment is recommended for patients with hepatic impairment.
- **Renal failure:** No dose adjustment is recommended for patients with renal impairment.
- **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:

Adverse Reactions Reported in 2% of Patients Treated with LINAUR and Greater than Placebo in Placebo-Controlled Clinical Studies of LINAUR Monotherapy or Combination Therapy are Nasopharyngitis, Diarrhea, Cough

When used in combination with specific anti-diabetic agents were: urinary tract infection and hypertriglyceridemia, when used as add-on to sulfonylurea; hyperlipidemia and weight increased, when used as add-on to pioglitazone; and constipation, when used add-on to basal insulin therapy.

Other adverse events are back pain, arthralgia, upper respiratory tract infection, headache, cough and pain in extremity, myalgia, pancreatitis, hypoglycemia.

4.9. Overdose

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

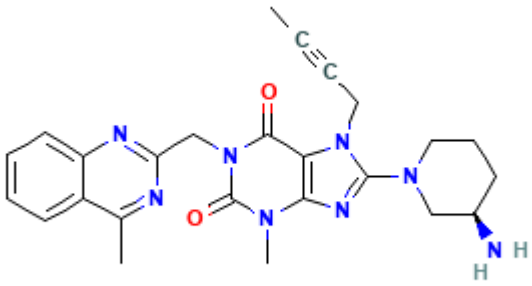
During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of LINAUR (equivalent to 120 times the recommended daily dose) there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

5. Pharmacological properties

LINAUR (linagliptin) tablets contain, 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:



5.1. Mechanism of action

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.

5.2. Pharmacodynamic properties

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

better regulation of glucose homeostasis. Linagliptin binds selectively to DPP-4, and selectively inhibits DPP4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

5.3. Pharmacokinetic properties

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (Tmax); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (Cmax) was 8.9 nmol/L.

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 prolonged elimination phase 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. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). 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.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced Cmax by 15% and increased AUC by 4%; this effect is not clinically relevant. LINAUR may be administered with or without food.

Distribution

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%-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.

Metabolism

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.

Excretion

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. Renal clearance at steady state was approximately 70 mL/min.

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 pack in Alu-Alu packing

8.4 Storage and handling instructions

Store 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

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

12. Date of revision: March 2024