Linaur™-E 10 , Linaur™-E 25

1. **Generic Name**

   Empagliflozin and Linagliptin Tablets (10 mg + 5 mg) and (25 mg + 5mg).

2. **Qualitative and Quantitative Composition**

   Each film coated tablet contains:

   Empagliflozin…….10/25 mg

   Linagliptin…….5 mg

   Excipients……q.s

3. **Dosage form and strength**

   Oral tablets containing Empagliflozin 10/25 mg and Linagliptin 5 mg.

4. **Clinical particulars**

   4.1 Therapeutic indication

   Linaur-E is a fixed dose combination of empagliflozin and linagliptin, is 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 starting dose is one film-coated tablet of Linaur-E 10 mg/5 mg (10 mg empagliflozin plus 5 mg linagliptin) once daily.
   - In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to one film-coated tablet of Linaur-E 25 mg/5 mg (25 mg empagliflozin plus 5 mg linagliptin) once daily.
   - When Linaur-E is used in combination with metformin, the metformin dose should be continued.
   - When Linaur-E is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonyl urea or insulin may be considered to reduce the risk of hypoglycaemia.

- Patients switching from empagliflozin (either 10 mg or 25 mg daily dose) and linagliptin (5 mg daily dose) to Linaur-E should receive the same daily dose of empagliflozin and linagliptin in the fixed dose combination as in separate tablets.

Missed doses

If a dose is missed, and it is 12 hours or more until the next dose, the dose should be taken as soon as the patient remembers. The next dose should be taken at the usual time. If a dose is missed, and it is less than 12 hours until the next dose, the dose should be skipped, and the next dose should be taken at the usual time. A double dose should not be taken to compensate for a forgotten dose.

4.3 Contraindication

- Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, or to any of the excipients present in the product.
- Severe renal impairment, end-stage renal disease, or dialysis.
- diabetic ketoacidosis (DKA)
- type 1 diabetes mellitus.

4.4 Special warnings and precautions for use

- *Diabetic ketoacidosis (DKA):* Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.
- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue Linaur-E.
- *Heart Failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of Linaur-E in patients who have known risk factors for heart failure. Monitor for signs and symptoms.

- *Hypotension:* Before initiating Linaur-E assess and correct volume status in patients with renal impairment, the elderly, in patients.
- *Cerebrovascular Accidents*: Caution should be observed in patients at high risk for cerebrovascular accidents
- Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalances.
- Renal impairment
- Hepatic injury
- Elevated haematocrit
- Necrotising fasciitis of the perineum (Fournier's gangrene)
- Chronic kidney disease
- Bullous pemphigoid
- Patients using Insulin
- Urinary Tract Infections (including urosepsis and pyelonephritis)

4.5 Drug interactions

Insulin and sulphonylureas

Insulin and sulphonylureas may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or sulphonylureas may be required to reduce the risk of hypoglycaemia when used in combination with Linaur-E.

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin

Linaur-E was not studied and is not indicated in combination with insulin. The use of linagliptin or empagliflozin in combination with insulin can increase the risk of hypoglycemia.

Pioglitazone

Linaur-E has not been studied in combination with pioglitazone and is therefore not indicated in combination with pioglitazone.

Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.

4.6 Use in special population

Paediatric: Safety and effectiveness of Linaur-E in pediatric patients under 18 years of age have not been established.

Geriatric: Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older.

Hepatic impairment: Linaur-E may be used in patients with hepatic impairment.

Renal failure: The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis.

Pregnancy and lactation: There are no data from the use of empagliflozin and linagliptin in pregnant women.

4.7 Effect on ability to drive and use machine

Linaur-E has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, when Linaur-E is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas).

4.8 Undesirable effects

Empagliflozin:

Metabolism: diabetic ketoacidosis

Skin and subcutaneous tissue disorders: Pruritus, rash, angioedema and urticaria.

Infections and infestations: Urinary tract infections, Necrotizing fasciitis of the perineum.

Others: Increased urination, Tubulointerstitial nephritis, Haematocrit increased, Serum lipids increased, Blood creatinine increased/Glomerular filtration rate decreased.

Linagliptin:

Hepatic/biliary/pancreatic: pancreatitis

Immune system disorders: angioedema, urticaria, hypersensitivity, Bullous pemphigoid.

Skin and subcutaneous tissue disorders: rash, bullous pemphigoid

Others: Nasopharyngitis, Diarrhoea, Cough, hypoglycaemia, thirst, back pain, arthralgia, upper respiratory tract infection, headache, cough and pain in extremity, myalgia, volume depletion, mouth ulceration, Amylase increased, Lipase increased.

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

4.9 Overdose

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

5. Pharmacological properties

5.1 Mechanism of action

Linaur-E combines two antihyperglycemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, DPP-4 inhibitor.

Empagliflozin

SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose and thereby increases urinary glucose excretion.

Linagliptin

Linagliptin is a potent, reversible and selective inhibitor of the enzyme DPP-4 which is involved in the inactivation of the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones are rapidly degraded by the

enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. GLP-1 and GIP are secreted by the intestine at a low basal level throughout the day and concentrations are increased in response to a meal. 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 production. Linagliptin binds to DPP-4 in a reversible manner and thus leads to an increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis.

5.2 Pharmacodynamic properties

Empagliflozin

Urinary Glucose Excretion: In patients with T2DM, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging approximately 64 grams p per day with empagliflozin 10 mg and 78 grams per day with empagliflozin 25 mg, once daily.

Urinary Volume: In a 5-day study, the mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg treatment.

Linagliptin

Linagliptin binds selectively to DPP-4 and exhibits a >10,000-fold selectivity versus closely related proteases DPP-8 or DPP-9 activity *in vitro*. At steady-state, plasma DPP-4 activity was inhibited over 24 h by more than 80% in most patients receiving linagliptin 5 mg once daily. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion.

Cardiac Electrophysiology:

Empagliflozin

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

In a randomized, placebo-controlled crossover study, 44 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), and placebo. No increase in the QTc, PR, or QRS intervals was observed with either the recommended dose of 5 mg or the 100 mg dose. A small increase in heart rate was seen at the linagliptin 100 mg dose, with a peak effect of about 4 bpm at 1 h post-dosing. No significant increase in heart rate was observed after the 5 mg therapeutic dose. The mean Cmax values were 7 nM for the single 5 mg dose and 267 nM for the single 100 mg dose.

5.3 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin are equivalent to the bioavailability of empagliflozin and linagliptin when administered as individual tablets.

Empagliflozin:

Absorption: After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.5 hours post dose.

The steady state mean plasma area under the concentration-time curve (AUC) and Cmax were 1,870 nmol.h and 259 nmol/L with empagliflozin 10 mg and 4,740 nmol.h and 687 nmol/L with empagliflozin 25 mg once daily.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on the population pharmacokinetic analysis.

Biotransformation

In vitro studies suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8 and UGT1A9.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 L/hour.

Linagliptin

Absorption

The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced Cmax by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin 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 1,110 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**.**

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.

Elimination

The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and linagliptin.

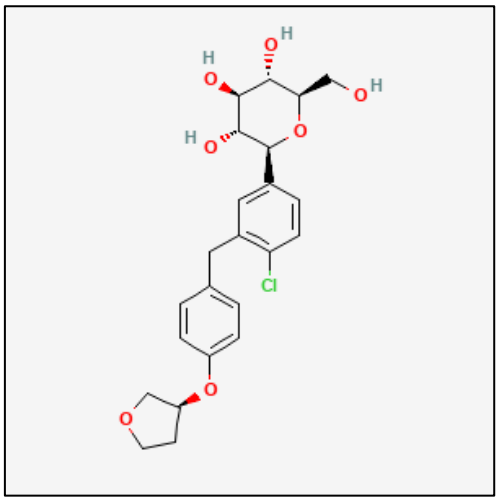
Focal areas of hepatocellular necrosis were found in the combination groups at ≥15: 30 mg/kg linagliptin: empagliflozin (3.8 times the clinical exposure for linagliptin and 7.8 times the clinical exposure for empagliflozin) as well as in the group treated with empagliflozin alone but not in the control group. The clinical relevance of this finding remains uncertain.

At exposures sufficiently more than exposure in humans after therapeutic doses, the combination of empagliflozin and linagliptin was not teratogenic and did not show maternal toxicity. Adverse effects on renal development were not observed after administration of empagliflozin alone, linagliptin alone or after administration of the combined products.

7. Description

Empagliflozin

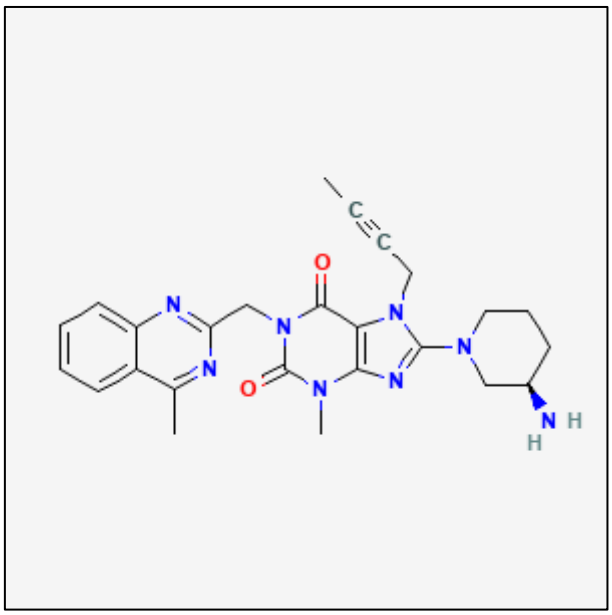
Empagliflozin inhibits sodium-glucose co-transporter 2 (SGLT2), the primary transporter responsible for glucose reabsorption in the kidney. Its chemical name is(2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-[[4-[(3*S*)-oxolan-3yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol. Its empirical formula is $C_{23}H_{27}ClO_7$ and its molecular weight is approximately 450.9 g/mol. The chemical structure of Empagliflozin is as follows:



Linagliptin:

Linagliptin is a DPP-4 inhibitor developed by Boehringer Ingelheim for the treatment of type II diabetes. The IUPAC name is 8-[(3*R*)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]purine-2,6-dione. Its empirical formula is $C_{25}H_{28}N_8O_2$ and its molecular weight is approximately 472.5 g/mol.

The chemical structure of Linagliptin is as follows:



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months

8.3 Packaging information

Linaur-E is available in strip of 10's.

8.4 Storage and handling instructions

Store in a dry place at a temperature not exceeding 30°C. Protect from light and moisture.

Keep medicine out of reach of children.

9. Patient Counselling Information

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

Patients are 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. Manufactured by

Lifecare Formulations Pvt. Ltd. (WHO-GMP Certified Company)
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11. Details of permission or license number with date

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12. Date of revision

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