Front

Linjardy

[Linagliptin + Empagliflozin]

TABLET

لنجارڈی

COMPOSITION:
Linjardy 5/10 Tablet:
Each film coated tablet contains:
Linagliptin ..... 5 mg.
Empagliflozin ..... 10 mg.

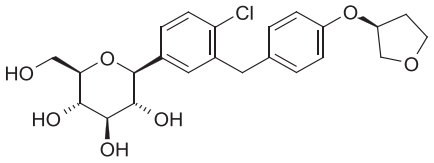
Product Specs.: Innovator

Linjardy 5/25 Tablet:
Each film coated tablet contains:
Linagliptin ..... 5 mg.
Empagliflozin ..... 25 mg.

Product Specs.: Innovator

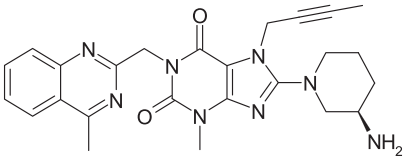
DESCRIPTION:
EMPAGLIFLOZIN AND LINAGLIPTIN COMBINATION tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and linagliptin.

Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter (SGLT2). The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3¬ furanyl] oxy] phenyl] methyl] phenyl]. The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Linagliptin is an orally-active 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. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.

Empagliflozin and Linagliptin Combination tablets for oral administration are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin. The inactive ingredients of Empagliflozin And Linagliptin Combination are the following: Tablet Core: mannitol, pregelatinized starch, corn starch, copovidone, copovidone, talc and magnesium stearate. Coating: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol and ferric oxide, yellow (10 mg/5 mg) or ferric oxide, red (25 mg/5 mg).

Mechanism of Action:
Empagliflozin And Linagliptin Combination combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.
Empagliflozin: Sodium-glucose co-transporter 2 (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 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.

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
The results of the bioequivalence study in healthy subjects demonstrated that Empagliflozin and Linagliptin Combination (25 mg empagliflozin/5 mg linagliptin) combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and linagliptin as individual tablets. Administration of the fixed-dose combination with food resulted in no change in overall exposure of empagliflozin or linagliptin; however, the peak exposure was decreased 39% and 32% for empagliflozin and linagliptin, respectively. These changes are not likely to be clinically significant.
Pharmacodynamics:
Empagliflozin: Urinary Glucose Excretion - in patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily.
Urinary Volume - In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.
Cardiac Electrophysiology - 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: 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.
Cardiac Electrophysiology In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

INDICATIONS:
Empagliflozin and Linagliptin Combination tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.

DOSAGE AND ADMINISTRATION:
Recommended dosage: The recommended dose of Empagliflozin and Linagliptin Combination is 10 mg empagliflozin/5 mg linagliptin

once daily in the morning, taken with or without food. In patients tolerating Empagliflozin and Linagliptin Combination, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.
In patients with volume depletion, correcting this condition prior to initiation of Empagliflozin and Linagliptin Combination is recommended.
No studies have been performed specifically examining the safety and efficacy of Empagliflozin and Linagliptin Combination in patients previously treated with other oral antihyperglycemic agents and switched to Empagliflozin and Linagliptin Combination. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

WARNINGS & PRECAUTIONS:
Pancreatitis: There have been post marketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue EMPAGLIFLOZIN AND LINAGLIPTIN COMBINATION and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Empagliflozin and Linagliptin Combination.
Hypotension: Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating Empagliflozin and Linagliptin Combination, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.
Renal impairment: Function Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients. Renal function should be evaluated prior to initiating Empagliflozin and Linagliptin Combination and periodically thereafter.
Hypoglycemia with concomitant use with insulin and insulin secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Empagliflozin and Linagliptin Combination.
Genital mycotic infections: Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.
Urinary tract infections: Empagliflozin increases the risk for urinary tract infections. Monitor and treat as appropriate.
Hypersensitivity reactions: There have been post-marketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of Empagliflozin and Linagliptin Combination). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Empagliflozin and Linagliptin Combination, assess for other potential causes for the event, and institute alternative treatment for diabetes.
Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Empagliflozin and Linagliptin Combination.
Increased low-Density lipoprotein cholesterol (LDL-C): Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.
Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Empagliflozin and Linagliptin Combination or any other antidiabetic drug.

ADVERSE REACTIONS:
See Warnings and Precautions

SPECIAL POPULATIONS:
Pregnancy: Pregnancy Category C Empagliflozin and Linagliptin Combination There are no adequate and well-controlled studies in pregnant women with Empagliflozin and Linagliptin Combination or its individual components. Empagliflozin and Linagliptin Combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing mothers: No studies in have been conducted with the combined components of Empagliflozin and Linagliptin Combination.
Pediatric use: Safety and effectiveness of Empagliflozin and Linagliptin Combination in pediatric patients under 18 years of age have not been established.
Geriatric use: Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older. 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.
Renal impairment: Empagliflozin The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations. The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.
Hepatic impairment: Empagliflozin and Linagliptin Combination may be used in patients with hepatic impairment.

CONTRAINDICATIONS:
Empagliflozin and Linagliptin Combination is contraindicated in patients with:
- Severe renal impairment, end-stage renal disease, or dialysis.
- A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity.
- History of serious hypersensitivity reaction to empagliflozin.

DRUG INTERACTIONS:
Diuretics: Co-administration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Insulin or insulin secretagogues: Co-administration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.
Positive urine glucose test monitoring: glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Drug interactions with linagliptin: 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. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Linjardy 5/10 Tablet	:	Pack of 2 x 7 tablets.
Linjardy 5/25 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 INFORMATIONS PLEASE CONTACT:

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