02-09-0409

Empagen-L

(Linagliptin and Empagliflozin) Tablets

Product Specifications: Innovator

Empagen-L 5mg/10mg Tablets: Each film coated tablet contains:

Linagliptin ..... 5 mg
Empagliflozin ..... 10 mg

Empagen-L 5mg/25mg Tablets: Each film coated tablet contains:

Linagliptin ..... 5 mg
Empagliflozin ..... 25 mg

DESCRIPTION: Empagen-L tablets 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 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Empagliflozin: Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (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]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.

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 regulating the glucose homeostasis.

CLINICAL PARTICULARS

Therapeutic indications: Empagen-L (empagliflozin and linagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or linagliptin, or in patients already being treated with both in free combination empagliflozin and linagliptin.

Limitations of Use: Empagen-L (empagliflozin and linagliptin) is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Posology and method of administration

Recommended Dosage: The recommended dose of Empagen-L is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. In patients tolerating Empagen-L (empagliflozin/linagliptin), 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/linagliptin tablets is recommended. Patients switching from empagliflozin (either 10 mg or 25 mg daily dose) and linagliptin (5 mg daily dose) should receive the same daily dose of empagliflozin/linagliptin tablets in the fixed dose combination as in separate tablets.

Recommended Dosage in Patients with Renal Impairment

- Assessment of renal function is recommended prior to initiation of empagliflozin/linagliptin tablets and periodically thereafter
- In patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or creatinine clearance (CrCl) ≥60 mL/min, no dose adjustment is required.
- In patients with an eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min empagliflozin/linagliptin tablets should not be initiated.
- Empagliflozin/linagliptin tablets should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2
- In patients with end-stage renal disease or in patients on dialysis, Empagliflozin/linagliptin tablets should not be used as empagliflozin is not expected to be effective in these patients

Recommended Dosage in Patients with Hepatic Impairment

- No dose adjustment is required in patients with mild to moderate hepatic impairment
- Empagliflozin/linagliptin tablets is not recommended for use in patients with severe hepatic impairment as Empagliflozin exposure is increased in these patients

Method of administration: Empagliflozin/linagliptin tablets are for oral use and can be taken with or without a meal at any time of the day at regular intervals. The tablets should be swallowed whole with water.

Contraindication

Empagliflozin/linagliptin tablets is contraindicated in patients with:

- Severe renal impairment, end-stage renal disease, or dialysis
- Hypersensitivity to empagliflozin, linagliptin, or any of its excipients, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyper-reactivity have occurred

WARNINGS AND PRECAUTIONS

Pancreatitis: Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In a cardiovascular and renal safety trial (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Empagliflozin/linagliptin tablets should be discontinued; if acute pancreatitis is confirmed, Empagliflozin/linagliptin tablets should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

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/linagliptin tablets, 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.

Impairment in Renal Function

- Empagliflozin causes intravascular volume contraction and increases serum creatinine and decreases eGFR. Before initiating Empagliflozin and Linagliptin tablets, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal impairment, heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing Empagliflozin and Linagliptin tablets in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue Empagliflozin and Linagliptin tablets promptly and institute treatment.
- Empagliflozin and Linagliptin tablets are not recommended when eGFR is persistently less than 45 mL/min/1.73 m2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.
- Renal function should be evaluated prior to initiation of Empagliflozin and Linagliptin tablets and monitored periodically thereafter.

Heart Failure: An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of Empagliflozin and Linagliptin tablets prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Empagliflozin and Linagliptin tablets.

Hepatic injury: Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

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 tablets.

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: Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Pyelonephritis and urosepsis were not reported from the clinical trials in patients treated with Empagliflozin and Linagliptin tablets. However, temporary interruption of Empagliflozin and Linagliptin tablets should be considered in patients with complicated urinary tract infections.

Ketoacidosis

- Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin.
- Empagliflozin and Linagliptin tablets should not be used for treatment of patients with type 1 diabetes
- The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level
- Before initiating Empagliflozin and Linagliptin tablets, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse
- In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately
- For patients who undergo scheduled surgery, consider temporarily discontinuing Empagliflozin and Linagliptin tablets for at least 3 days prior to surgery
- Consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin and Linagliptin tablets in other clinical situations known to predispose to ketoacidosis (e.g., a prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Empagliflozin and Linagliptin tablets
- Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin and Linagliptin tablets and seek medical attention immediately if signs and symptoms occur

Elderly: A higher risk of volume depletion adverse reactions were reported in patients aged 75 years and older, treated with empagliflozin, especially at 25 mg/day. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Empagliflozin and Linagliptin tablets should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors.

Elevated haematocrit: Haematocrit increase was observed with empagliflozin treatment

Risk for volume depletion: Caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy (e.g. thiazide and loop diuretics) with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with Empagliflozin and Linagliptin tablets should be considered until the fluid loss is corrected.

Severe and Disabling Arthralgia: There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors.

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.

USE IN SPECIFIC POPULATIONS

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

Animal studies with empagliflozin have shown adverse effects on postnatal development. As a precautionary measure it is preferable to avoid the use of Empagliflozin and Linagliptin tablets during pregnancy.

Nursing Mothers

No data in humans are available on excretion of empagliflozin and linagliptin into milk. A risk to newborns or infants cannot be excluded. Empagliflozin and Linagliptin tablets should not be used during breast-feeding because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development.

Fertility: No trials on the effect on human fertility have been conducted with Empagliflozin and Linagliptin tablets or with the individual active substances.

Pediatric Use: Safety and effectiveness of Empagliflozin and Linagliptin tablets 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.

Hepatic Impairment

Empagliflozin and Linagliptin tablets may be used in patients with hepatic impairment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Empagliflozin and Linagliptin tablets 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, in particular when Empagliflozin and Linagliptin tablets is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas).

DRUG INTERACTIONS

Drug Interactions with Empagliflozin

Diuretic: Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

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

Insulin or Insulin Secretagogues

Coadministration of Empagliflozin and Linagliptin tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Adverse Reactions

Heart Failure, Hypotension, Acute Kidney Injury, Severe and Disabling Arthralgia

Urinary tract infection (including pyelonephritis and urosepsis), Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, Nasopharyngitis, Necrotising fasciitis of the perineum (Fournier´s gangrene)

Hypoglycaemia (when used with sulphonylurea or insulin), Thirst, Diabetic ketoacidosis, Volume depletion, Increased urination, Dysuria, Cough, Pancreatitis, Pruritus, Rash, Bullous pemphigoid.

Amylase, lipase, serum lipids and hematocrit increased

Blood creatinine increased/Glomerular filtration rate decreased

OVERDOSAGE

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.

The removal of empagliflozin by haemodialysis has not been studied. Linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis.

CLINICAL PHARMACOLOGY

Mechanism of Action: Empagen-L 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: 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: 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

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 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.

Pharmacokinetics

Empagliflozin

Absorption: After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose.

Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide).

Elimination: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

Linagliptin

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.

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% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin.

Metabolism: Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway.

Elimination: 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.

Specific Populations

Renal Impairment: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin tablets after administration in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m2), and severe (eGFR: less than 30 mL/min/1.73 m2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function.

Linagliptin: In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased (AUCτ,ss by 71% and Cmax by 46%) compared with healthy subjects. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in AUCτ,ss by 42% and Cmax by 35%). For both type 2 diabetes groups, renal excretion was below 7% of the administered dose.

Hepatic Impairment: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administering empagliflozin and linagliptin combination in hepatically impaired patients have not been performed.

Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75% and Cmax increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure (AUCτ,ss) of linagliptin was approximately 25% lower and Cmax,ss was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUCss of linagliptin was about 14% lower and Cmax,ss was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (ChildPugh class C) had comparable exposure of linagliptin in terms of AUC0-24 and approximately 23% lower Cmax compared with healthy subjects.

Effects of Age, Body Mass Index, Gender, and Race

No clinically relevant difference in pharmacokinetics of empagliflozin and linagliptin were seen.

Pediatric

Empagliflozin: A paediatric Phase 1 trial examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Linagliptin: A paediatric Phase 2 trial examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

HOW SUPPLIED:

Empagen-L 5mg/10mg Tablets: Pack of 14 Tablets

Empagen-L 5mg/25mg Tablets: Pack of 14 Tablets

STORAGE

Do not store above 25ºC.

The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from moisture, light and reach of children.

To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:

FEROZSONS LABORATORIES LIMITED

P. O. Ferozsons, Nowshera-Pakistan

Mfg. Lic. No. 000038