EMPAGEN

4000002904

(Empagliflozin Tablets)

Product Specifications: Innovator
Empagen Tablets 10 mg:
Each film coated tablet contains: Empagliflozin ..... 10 mg
Product contains Lactose
Empagen Tablets 25 mg:
Each film coated tablet contains: Empagliflozin ..... 25 mg
Product contains Lactose

DESCRIPTION

Empagen tablets for oral use contain Empagliflozin, an 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.

PHARMACEUTICAL FORM:

Film coated tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

Empagen (Empagliflozin) is indicated:

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
- to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
- as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.
- in adults for the treatment of chronic kidney disease.

Limitations of Use

Empagen (Empagliflozin) is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

In patients with an eGFR <60 ml/min/1,73 m2 the daily dose of empagliflozin is 10 mg.

Empagen (Empagliflozin) is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1,73 m^2. Empagen (Empagliflozin) is likely to be ineffective in this setting based upon its mechanism of action.

POSOLOGY AND METHOD OF ADMINISTRATION

Prior to Initiation of Empagen (Empagliflozin)

- Assess renal function before initiating Empagen (Empagliflozin) and as clinically indicated.
- In patients with volume depletion, correct this condition before initiating Empagen (Empagliflozin).

Recommended Dosage

The recommended dosage of Empagen (Empagliflozin) in adult and pediatric patients aged 10 years and older.

Population	Indication	Recommended Dosage
Adults	Reduce the risk of cardiovascular death and hospitalization in patients with heart failure	• 10 mg orally once daily in the morning, taken with or without food. • Data are insufficient to provide a dosage recommendation in patients who have: • type 2 diabetes mellitus and established cardiovascular disease with an eGFR less than 30 mL/min/1,73 m^2 • o heart failure with an eGFR less than 20 mL/min/1,73 m2
	Reduce the risk of cardiovascular death in patients with type 2 diabetes mellitus with established cardiovascular disease	
	Chronic kidney disease	• The recommended dose is 10 mg empagliflozin once daily.
Adults & Pediatric patients aged 10 years and older	Glycemic control in type 2 diabetes mellitus	• 10 mg orally once daily in the morning, taken with or without food. • For additional glycemic control, may increase to 25 mg orally once daily in patients tolerating 10 mg once daily who have an eGFR ≥60 ml/min/1,73 m2

Recommendations Regarding Missed Dose

• If a dose is missed, instruct patients to take the dose as soon as possible.
• Do not double up the next dose.

Method of Administration

The tablets can be taken with or without food, swallowed whole with water.

CONTRAINDICATIONS

Empagliflozin is contraindicated in patients with:

- Hypersensitivity to Empagliflozin or any of the excipients of the product, reactions such as angioedema have occurred.
- Patients on dialysis.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including Empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking Empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Empagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Empagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with Empagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Empagliflozin should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the post-marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Empagliflozin, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing Empagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Empagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including Empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1,73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Empagliflozin in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. In Adults patient the risk of hypoglycemia is increased when Empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. In pediatric patients aged 10 years and older, the risk of hypoglycemia was higher with empagliflozin regardless of insulin use. 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. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including Empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Empagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Empagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

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.

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment.

Chronic kidney disease

Patients with albuminuria may benefit more from treatment with empagliflozin.

Infiltrative disease or Takotsubo cardiomyopathy

Patients with infiltrative disease or with Takotsubo cardiomyopathy have not been specifically studied. Therefore, efficacy in these patients has not been established.

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 genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions (e.g., angioedema) in patients treated with Empagliflozin. If a hypersensitivity reaction occurs, discontinue Empagliflozin; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin is contraindicated in patients with hypersensitivity to Empagliflozin or any of the excipients.

Lactose

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

INTERACTION WITH OTHER MEDICINAL PRODUCTS

Table 1: Clinically Relevant Interactions with Empagliflozin.

Diuretics	
Clinical Impact	Co-administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating Empagliflozin, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when Empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Co-administration of Empagliflozin 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.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during Empagliflozin initiation and dosage changes.

Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.
Inducers of UGT enzymes	
Clinical Impact	The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy.
Intervention	If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to empagliflozin is appropriate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on animal data showing adverse renal effects, Empagliflozin is not recommended during the second and third trimesters of pregnancy. The limited available data with Empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Nursing Mothers

There is limited information regarding the presence of Empagliflozin in human milk, the effects on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for Empagliflozin to affect postnatal renal development, advise patients that use of Empagliflozin is not recommended while breastfeeding.

Pediatric Use

The safety and effectiveness of empagliflozin as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. The safety profile of pediatric patients treated with empagliflozin was similar to that observed in adults with type 2 diabetes mellitus, with the exception of hypoglycemia risk which was higher in pediatric patients treated with empagliflozin regardless of concomitant insulin use. The safety and effectiveness of empagliflozin have not been established in pediatric patients less than 10 years of age.

Geriatric Use

Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment. The risk of urinary tract infections and volume depletion-related adverse reactions increased in patients who were 75 years of age and older.

In heart failure studies, safety and efficacy were similar for patients 65 years and younger and those older than 65 years.

Renal impairment

In clinical trials, 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. Use of Empagliflozin for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m^2.

In a large cardiovascular outcomes study of patients with type 2 diabetes and established cardiovascular disease, the cardiovascular death findings were consistent with the overall findings.

No dose adjustment is recommended for heart failure patients. There are insufficient data to support a dosing recommendation in patients with eGFR below 20 mL/min/1.73 m^2. In the trial of pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, patients with an eGFR less than 60 mL/min/1.73 m2 were not enrolled.

Empagliflozin is contraindicated in patients on dialysis.

Hepatic impairment

Empagliflozin may be used in patients with hepatic impairment. No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

UNDESIRABLE EFFECTS

Summary of the safety profile

Type 2 diabetes mellitus

The overall incidence of adverse events in patients treated with Empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycemia when used with sulphonylurea or insulin.

Heart failure

The most frequent adverse reaction was volume depletion.

Chronic kidney disease

The most frequent adverse events were gout and acute kidney injury which were more frequently reported in patients on placebo.

The overall safety profile of Empagliflozin was generally consistent across the studied indications.

Very Common (≥1/10): Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, Urinary tract infection (including pyelonephritis and urosepsis), Hypoglycemia (when used with sulphonylurea or insulin), Volume depletion,

Common (≥1/100 to <1/10): Thirst, Constipation, Pruritus (generalised), Rash, Increased urination, Serum lipids increased.

Uncommon (≥1/1 000 to <1/100): Diabetic ketoacidosis, Urticaria, Angioedema, Dysuria, Blood creatinine increased/ Glomerular filtration rate decreased, Haematocrit increased.

Rare (≥1/10 000 to <1/1 000): Necrotising fasciitis of the perineum (Fournier's gangrene),

Very Rare (<1/10 000): Tubulo-interstitial nephritis.

OVERDOSAGE

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of Empagliflozin by hemodialysis has not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Empagliflozin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when Empagliflozin is used in combination with a sulphonylurea and/or insulin.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

MECHANISM OF ACTION

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, Empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions such as lowering both pre-and afterload of the heart and down-regulating sympathetic activity.

PHARMACODYNAMICS PROPERTIES

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. Data from single oral doses of Empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

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.

PHARMACOKINETIC PROPERTIES

Absorption

After oral administration, peak plasma concentrations of Empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Administration of 25 mg Empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on Empagliflozin pharmacokinetics was not considered clinically relevant and Empagliflozin may be administered with or without food.

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 [^{14}C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

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. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with Empagliflozin half-life.

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). Systemic exposure of each metabolite was less than 10% of total drug-related material.

Excretion

Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

SPECIFIC POPULATIONS

Pediatric Patients

The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

HOW SUPPLIED

Empagen Tablet 10 mg: Pack of 14 Tablets

Empagen Tablet 25 mg: Pack of 14 Tablets

STORAGE

Do not store above 30°C.

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