Erli®
(EMPAGLIFLOZIN)

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COMPOSITION
Erli 10mg Tablets:
Each film-coated tablet contains:
Empagliflozin.....10 mg
Erli 25mg Tablets:
Each film-coated tablet contains:
Empagliflozin.....25 mg
(As per innovator's specs.)

DESCRIPTION
Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, lowers the renal threshold for glucose and increases urinary glucose excretion by interfering with the reabsorption of renally-filtered glucose across the tubular lumen of the proximal renal tubules. Empagliflozin decreases fasting and post-prandial blood glucose levels, and imparts a low risk of hypoglycemia as its mechanism of action is independent of beta cell function and insulin pathway.

CLINICAL PHARMACOLOGY

Mechanism of Action
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.

Pharmacodynamics
Urinary Glucose Excretion
In patients with type 2 diabetes, urinary glucose excretion increases immediately following a dose of Empagliflozin and is 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 patients treated for 5 days, mean 24-hour urine volume increases from baseline was 341 mL on Day 1 and 135 mL on Day 5 of Empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology
After administration of a single oral dose of Empagliflozin 25 mg, Empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, no increase in QTc might be observed with either 25 mg or 200 mg Empagliflozin.

Pharmacokinetics
Absorption
After oral administration, peak plasma concentrations of Empagliflozin are reached at 1.5 hours post-dose. Thereafter, plasma concentrations decline in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and Cmax are 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg Empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg Empagliflozin once daily treatment. Systemic exposure of Empagliflozin increases in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin are similar, suggesting linear pharmacokinetics with respect to time. 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 Cmax decreased by approximately 37%, compared to fasted condition. The effect of food on Empagliflozin pharmacokinetics is not clinically relevant and Empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution is estimated to be 73.8 L. Following administration of an oral [14C]-Empagliflozin solution to healthy patients, the red blood cell partitioning is approximately 36.8% and plasma protein binding is 86.2%

Metabolism
No major metabolites of Empagliflozin may be detected in human plasma and the most abundant metabolites ate three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite is less than 10% of total drug-related material. The primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination
The apparent terminal elimination half-life of Empagliflozin is estimated to be 12.4 h and apparent oral clearance is 10.6 L/h. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, may be observed at steady-state, which is consistent with Empagliflozin half-life. Following administration of an oral [14C]-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 is unchanged parent drug and approximately half of drug-related radioactivity excreted in urine is unchanged parent drug.

Pharmacokinetics in special populations
Renal Impairment
In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of Empagliflozin increases by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of Empagliflozin are similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of Empagliflozin are roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The apparent oral clearance of Empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of Empagliflozin that is excreted unchanged in urine, and urinary glucose excretion, declines with decrease in eGFR.

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

Pediatric
There are no studies conducted in patients under the age of 10. In pateints ≥10 to <18 years of age with type 2 diabetes mellitus studies show that pharmacokinetic responses are in consistency with that observed in adult subjects.

INDICATIONS
Erli is indicated for
• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
• To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use
Erli is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION
Adult dosage
The recommended dose of Erli is 10 mg once daily in the morning, taken with or without food. In patients tolerating Erli, the dose may be increased to 25 mg.
In patients with volume depletion, correcting this condition prior to initiation of Erli is recommended.

Dosage adjustment
Assessment of renal function is recommended prior to initiation of Erli and periodically thereafter. Erli should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2. Erli should be discontinued if eGFR is less than 45 mL/min/1.73 m^2.

CONTRAINDICATIONS
• History of serious hypersensitivity reaction to Erli
• Severe renal impairment, end-stage renal disease, or dialysis

WARNING AND PRECAUTIONS

Hypotension
Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating Erli particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating Empagliflozin, 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.

Ketoacidosis
Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization may occur in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including Empagliflozin. 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.
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. In patients treated with Empagliflozin consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute Kidney Injury and Impairment in Renal Function
Empagliflozin causes intravascular volume contraction and can cause renal impairment. Acute kidney injury may occur, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including Empagliflozin; it might also occur in patients younger than 65 years of age.
Before initiating Empagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing Empagliflozin 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 promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating. Renal function should be evaluated prior to initiation of Empagliflozin and monitored periodically thereafter. Frequent renal function monitoring is recommended in patients who are renally compromised. Use of Empagliflozin is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis
Serious urinary tract infections may occur 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. The risk of hypoglycemia is increased when Empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.

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.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with Empagliflozin. Monitor and treat as appropriate.

Hypersensitivity reactions
Hypersensitivity reactions like angioedema have been reported with the use of empagliflozin. Monitoring is recommended and empagliflozin should be discontinued if signs of hypersensitivity appear.

Fracture risk factors
SGLT2 inhibitors e.g. empagliflozin should be avoided in patients with fracture risk factors as increased incidence of bone fractures may occur with their use.

ADVERSE REACTIONS
Infections and infestations
Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, Urinary tract infection (including pyelonephritis and urosepsis)
Metabolism and nutrition disorders
Very common: Hypoglycaemia (when used with sulphonylurea or insulin)
Common: Thirst
Rare: Diabetic ketoacidosis
Skin and subcutaneous tissue disorders
Common: Pruritus (generalised), Rash
Uncommon: Urticaria
Not known: Angioedema
Vascular disorders
Uncommon: Volume depletion
Renal and urinary disorders
Common: Increased urination
Uncommon: Dysuria
Investigations
Common: Serum lipids increased
Uncommon: Blood creatinine increased/Glomerular filtration rate decreased, Haematocrit increased

DRUG INTERACTIONS
Diuretics
Coadministration of Empagliflozin with diuretics results in increased urine volume and frequency of voids, which might enhance the potential for volume depletion
Insulin or Insulin Secretagogues
Coadministration 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.

USE IN SPECIAL POPULATIONS
Pregnancy
Empagliflozin is not recommended during the second and third trimesters of pregnancy. Limited data available 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. It should be only be used during pregnancy if the potential benefit justifies the potential risk to the fetus

Nursing mother
There is no information regarding the presence of Empagliflozin in human milk, the effects of Empagliflozin on the breastfed infant or the effects on milk production. 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, therefore, Empagliflozin is not recommended while breastfeeding.

Pediatrics
The safety and effectiveness of Empagliflozin in pediatric patients under 18 years of age have not been established.

Elderly
No Empagliflozin dosage change is recommended based on age.

Renal impairment
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. It is observed that glucose lowering benefit of empagliflozin is 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 may be used in patients with hepatic impairment

OVER DOSAGE
In the event of an overdose with Empagliflozin employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of Empagliflozin by hemodialysis has not been studied.

PRESENTATION
Erli 10mg : Pack of 14 Tablets
Erli 25mg : Pack of 14 Tablets

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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