EGLARO®
(Ertugliflozin)

اِگلیرو

COMPOSITION
Each film coated tablet contains:
Ertugliflozin L-Pyroglutamic Acid eq to Ertugliflozin... ... 5mg

Each film coated tablet contains:
Ertugliflozin L-Pyroglutamic Acid eq to Erfugliflozin... ... l5mg
(As per innovator's specs.)

DESCRIPTION
Eglaro (ertugliflozin) tablets for oral use contain ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor.

The chemical name of ertugliflozin L-pyroglutamic acid is (1S,2S,3S,4R,5S)-5-(4-chloro-3-(4ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2S)-5oxopyrrolidine-2-carboxylic acid. The molecular formula is $C_{27}H_{32}ClNO_{10}$ and the molecular weight is 566.00.

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

Pharmacodynamics
Urinary Glucose Excretion and Urinary Volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single-and multiple-dose administration of ertugliflozin. Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE). Enhanced UGE is maintained after multiple-dose administration. UGE with ertugliflozin also results in increases in urinary volume.

Pharmacokinetics
The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes mellitus. The steady state mean plasma AUC and Cmax were 398 ng·hr/mL and 81.3 ng/mL, respectively, with 5 mg ertugliflozin once-daily treatment, and 1,193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg ertugliflozin once-daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median Tmax) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma Cmax and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg (0.1 times the lowest recommended dose) to 300 mg (20 times the highest recommended dose) and following multiple doses from 1 mg (0.2 times the lowest recommended dose) to 100 mg (6.7 times the highest recommended dose). The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%.

Distribution
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 85.5 L. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Metabolism
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Excretion
The mean systemic plasma clearance following an intravenous 100 µg dose was 11.2 L/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours based on the population pharmacokinetic analysis. Following administration of an oral [14C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Pharmacokinetics in special populations
Patients with Renal Impairment
In a clinical pharmacology study in patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15mg ertugliflozin, the mean increases in AUC of ertugliflozin were 1.6-, 1.7-, and 1.6-fold, respectively, for mild, moderate and severe renally impaired patients, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically meaningful. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Patients with Hepatic Impairment
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and Cmax decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

Effects of Age, Body Weight, Gender, and Race
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

INDICATIONS
Eglaro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:
• as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
• in addition to other medicinal products for the treatment of diabetes.

DOSAGE AND ADMINISTRATION
Adult dosage
Prior to Initiation of Eglaro.
• Assess renal function prior to initiation of Eglaro.
• In patients with volume depletion, correct this condition before initiating Eglaro.

Recommended Dosage
• The recommended starting dose of Eglaro is 5 mg once daily, taken in the morning, with or without food.
• For additional glycemic control, the dose may be increased to 15 mg once daily in patients tolerating Eglaro.

Dosage adjustment
Renal impairment
Assessment of renal function is recommended prior to initiation of Eglaro and periodically thereafter.

Initiation of Eglaro is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 or CrCl less than 60 ml/min.

Eglaro should be discontinued when eGFR is persistently less than 45 ml/min/1.73 m2 or CrCl is persistently less than 45 ml/min.

Eglaro should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as it is not expected to be effective in these patients.

Hepatic impairment
No dose adjustment of ertugliflozin is necessary in patients with mild or moderate hepatic impairment. Ertugliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

Elderly (≥ 65 years old)
No dose adjustment of ertugliflozin is recommended based on age.

Paediatric population
The safety and efficacy of ertugliflozin in children under 18 years of age have not been established. No data are available.

CONTRAINDICATIONS
• Hypersensitivity to ertugliflozin or any excipient in Eglaro, reactions such as angioedema have occurred.
• Patients on dialysis.

WARNING AND PRECAUTIONS
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 ertugliflozin. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors.

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. The risk of ketoacidosis may be greater with higher doses. Ertugliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with ertugliflozin 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 ertugliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, ertugliflozin 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 reported cases, 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 ertugliflozin, 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 ertugliflozin for at least 4 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing ertugliflozin 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 ertugliflozin.

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

Lower Limb Amputation
In a long-term cardiovascular outcomes study, in patients with type 2 diabetes and established cardiovascular disease, the occurrence of non-traumatic lower limb amputations was reported with event rates of 4.7, 5.7, and 6.0 events per 1000 patient-years in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms, respectively.

Amputation of the toe and foot were most frequent (81 out of 109 patients with lower limb amputations). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. Patients with amputations were more likely to be male, have higher A1C (%) at baseline, have a history of peripheral arterial disease, amputation or peripheral revascularization procedure, diabetic foot, and to have been taking diuretics or insulin.

Across seven ertugliflozin clinical trials, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the ertugliflozin 5 mg group, and 8 (0.5%) patients in the ertugliflozin 15 mg group.

Before initiating ertugliflozin, consider factors in the patient history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving ertugliflozin for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue ertugliflozin if these complications occur.

Volume Depletion
Ertugliflozin can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including ertugliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, patients with low systolic blood pressure, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating ertugliflozin 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 ertugliflozin. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. 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 (e.g., sulfonylurea) are known to cause hypoglycemia. Ertugliflozin may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ertugliflozin.

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 postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including ertugliflozin. Cases have been reported in females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with ertugliflozin 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 ertugliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections
Ertugliflozin increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections. Monitor and treat appropriately.

ADVERSE REACTIONS
Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System Organ Class Frequency	Adverse Reaction
Infections and infestations	
Very common	Vulvovaginal mycotic infection and other female genital mycotic infections
Common	Balanitis candida and other male genital mycotic infections
Not known	Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Rare	Diabetic ketoacidosis
Vascular disorders	
Common	Volume depletion
Renal and urinary disorders	
Common	Increased urination
Uncommon	Dysuria, Blood creatinine increased/Glomerular filtration rate decreased
Reproductive system and breast disorders	
Common	Vulvovaginal pruritus
General disorders and administration site conditions	
Common	Thirst
Investigations	
Common	Serum lipids changed, Haemoglobin increased, BUN increased

DRUG INTERACTIONS

Pharmacodynamic interactions

Diuretics

Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with ertugliflozin.

Pharmacokinetic interactions

Effects of other medicinal products on the pharmacokinetics of ertugliflozin

Metabolism by UGT1A9 and UGT2B7 is the primary clearance mechanism for ertugliflozin. Interaction studies conducted in healthy subjects, using a single dose design, suggest that the pharmacokinetics of ertugliflozin are not altered by sitagliptin, metformin, glimepiride, or simvastatin.

Multiple-dose administration of rifampin (a UGT and CYP inducer) decreases ertugliflozin AUC and Cmax by 39% and 15%, respectively. This decrease in exposure is not considered clinically relevant and therefore, no dose adjustment is recommended. A clinically relevant effect with other inducers (e.g., carbamazepine, phenytoin, phenobarbital) is not expected.

The impact of UGT inhibitors on the pharmacokinetics of ertugliflozin has not been studied clinically, but potential increase in ertugliflozin exposure due to UGT inhibition is not considered to be clinically relevant.

Effects of ertugliflozin on the pharmacokinetics of other medicinal products

Interaction studies conducted in healthy volunteers suggest that ertugliflozin had no clinically relevant effect on the pharmacokinetics of sitagliptin, metformin, and glimepiride.

Coadministration of simvastatin with ertugliflozin resulted in a 24% and 19% increase in AUC and Cmax of simvastatin, respectively, and 30% and 16% increase in AUC and Cmax of simvastatin acid, respectively. The mechanism for the small increases in simvastatin and simvastatin acid is unknown and is not perpetrated through OATP inhibition by ertugliflozin. These increases are not considered to be clinically meaningful.

USE IN SPECIAL POPULATIONS

Pregnancy

There are limited data from the use of ertugliflozin in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation. Therefore, should not be used during pregnancy.

Nursing mother

There is no information regarding the presence of ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats and caused effects in the offspring of lactating rats. Pharmacologically-mediated effects were observed in juvenile rats. Since human kidney maturation occurs in utero and during the first 2 years of life when exposure from breast-feeding may occur, a risk to newborns/infants cannot be excluded. Ertugliflozin should not be used during breast-feeding.

Pediatrics

The safety and efficacy of ertugliflozin in children under 18 years of age have not been established. No data are available.

Elderly

No dose adjustment of ertugliflozin is recommended based on age.

Renal impairment

Eglaro is contraindicated in patients on dialysis. No dosage adjustment is needed in patients with eGFR ≥45 mL/min/1.73 m2.

Hepatic impairment

No dose adjustment of ertugliflozin is necessary in patients with mild or moderate hepatic impairment. Ertugliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

OVER DOSAGE

Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

In the event of an overdose, 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 ertugliflozin by haemodialysis has not been studied.

PRESENTATION

Eglaro 5mg : Pack of 14 tablets.
Eglaro 15mg : 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
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