02-09-0404

Ertuvia

(Ertugliflozin Tablets)

Product Specifications: Innovator
Ertuvia 5 mg Tablets
Each film coated tablet contains: Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin …… 5 mg
Ertuvia 15 mg Tablets
Each film coated tablet contains: Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin …… 15 mg
Product contains Lactose

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

CLINICAL PARTICULARS
Therapeutic indications
Ertuvia (ertugliflozin) tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use
Ertuvia (ertugliflozin) is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
Posology and method of administration
Recommended Dosage
- The recommended starting dose of Ertuvia (ertugliflozin) is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Ertuvia (ertugliflozin) 5 mg once daily, the dose may be increased to a maximum recommended dose of 15 mg once daily if additional glycemic control is needed.
- In patients with volume depletion, correct this condition prior to initiation of Ertuvia (ertugliflozin).

Patients with Renal Impairment
- Assess renal function prior to initiation of Ertuvia (ertugliflozin) and periodically thereafter.
- Use of Ertuvia (ertugliflozin) is contraindicated in patients with an eGFR less than 30mL/minute/1.73m^2.
- Initiation of Ertuvia (ertugliflozin) is not recommended in patients with an eGFR of 30mL/minute/1.73m^2 to less than 60 mL/minute/1.73 m^2.
- Continued use of Ertuvia (ertugliflozin) is not recommended when eGFR is persistently between 30 and less than 60 mL/minute/1.73 m^2.

No dose adjustment is needed in patients with mild renal impairment.
Method of administration
Ertugliflozin may be administered with or without food.
Contraindication
- Severe renal impairment, end-stage renal disease (ESRD), or dialysis.
- History of a serious hypersensitivity reaction to ertugliflozin tablets.

WARNINGS AND PRECAUTIONS
Hypotension
Ertugliflozin tablet causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating ertugliflozin tablets particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients (≥65 years), in patients with low systolic blood pressure, and in patients on diuretics. Before initiating ertugliflozin tablets, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.
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 and cases have been reported in Ertugliflozin-treated patients in clinical trials. Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) of Ertugliflozin-treated patients and 0% of comparator-treated patients. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. Ertugliflozin tablets is not indicated for the treatment of patients with type 1 diabetes mellitus.
Patients treated with Ertugliflozin tablets 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 tablets may be present even if blood glucose levels are less than
250 mg/dL. If ketoacidosis is suspected, Ertugliflozin tablets 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.
Acute Kidney Injury and Impairment in Renal Function
Ertugliflozin causes intravascular volume contraction and can cause renal impairment. There have been post marketing reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors.
Before initiating Ertugliflozin, 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 Ertugliflozin 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 Ertugliflozin promptly and institute treatment.
Ertugliflozin increases serum creatinine and decreases eGFR. Patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) may be more susceptible to these changes. Renal function abnormalities can occur after initiating Ertugliflozin. Renal function should be evaluated prior to initiating Ertugliflozin and periodically thereafter. Use of Ertugliflozin is not recommended when eGFR is persistently between 30 and less than 60 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
There have been post marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors. Cases of pyelonephritis also have been reported in Ertugliflozin -treated patients in clinical trials. 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.
Lower Limb Amputation
An increased risk for lower limb amputation (primarily of the toe) has been observed in clinical studies with another SGLT2 inhibitor. Across seven Phase 3 clinical trials in the Ertugliflozin development program, 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. A causal association between Ertugliflozin and lower limb amputation has not been definitively established.
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.
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 post marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors. 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.
Increases in Low-Density Lipoprotein Cholesterol (LDL-C)
Dose-related increases in LDL-C can occur with Ertugliflozin. Monitor and treat as appropriate.
Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Ertugliflozin.

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on animal data showing adverse renal effects, Ertugliflozin is not recommended during the second and third trimesters of pregnancy.
The limited available data with Ertugliflozin in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy
Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Poorly-controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.
Lactation
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. 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, advise women that the use of Ertugliflozin is not recommended while breastfeeding.
Pediatric Use
Safety and effectiveness of Ertugliflozin in pediatric patients under 18 years of age have not been established.

Geriatric Use
No dosage adjustment of Ertugliflozin is recommended based on age.
Renal Impairment
The safety and efficacy of Ertugliflozin have not been established in patients with type 2 diabetes mellitus and moderate renal impairment. Compared to placebo-treated patients, patients with moderate renal impairment treated with Ertugliflozin did not have improvement in glycemic control, and had increased risks for renal impairment, renal-related adverse reactions and volume depletion adverse reactions. Therefore, Ertugliflozin is not recommended in this population.
Ertugliflozin is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. Ertugliflozin is not expected to be effective in these patient populations.
No dosage adjustment or increased monitoring is needed in patients with mild renal impairment.
Hepatic Impairment
No dosage 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 this patient population.

Drug Interactions

Concomitant Use with Insulin and Insulin Secretagogues
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.
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.

Adverse Reactions

The following important adverse reactions are described below and elsewhere in the labeling related to ertugliflozin:

- Hypotension
- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function
- Urosepsis and Pyelonephritis
- Lower Limb Amputation
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Genital Mycotic Infections
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C)

Post Marketing Experience

Additional adverse reactions have been identified during post approval use of ertugliflozin**.** Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cases of necrotizing fasciitis of the perineum (Fournier's gangrene) have been seen with SGLT2 inhibitors.

OVERDOSAGE

In the event of an overdose with Ertugliflozin, employ the usual supportive measures as dictated by the patient's clinical status. Removal of ertugliflozin by hemodialysis has not been studied.

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.
Cardiac Electrophysiology
The effect of Ertugliflozin on QTc interval was evaluated in a Phase 1 randomized, placebo- and positive-controlled 3-period crossover study in 42 healthy subjects. At 6.7 times the therapeutic exposures with maximum recommended dose, Ertugliflozin does not prolong QTc to any clinically relevant extent.

Pharmacokinetics

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes mellitus. The steady state mean plasma AUC and C_{max} 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 T_{max}) of ertugliflozin occur at 1 hour postdose under fasted conditions. Plasma C_{max} 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%.
Effect of Food
Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour, but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, ertugliflozin was administered without regard to meals.
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.
Elimination
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 [^{14}C]-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.
Specific Populations
Patients with Renal Impairment
In a Phase 1 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 15 mg 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 C_{max} 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.
Pediatric Patients
No studies with ertugliflozin have been performed in pediatric patients.
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.

HOW SUPPLIED

Ertuvia 5 mg Tablets: Pack of 14 Tablets
Ertuvia 15 mg Tablets: Pack of 14 Tablets

STORAGE

Do not store above 25°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:
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