# Ertuget™

[ErtugIifIozin]

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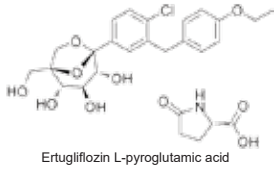
5mg & 15mg Tablets

**DESCRIPTION**

Ertuget Tablets for oral use contains Ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor. Ertugliflozin belongs to the class of potent and selective inhibitors of the sodium-dependent glucose cotransporters (SGLT), more specifically the type 2 which is responsible for about 90% of the glucose reabsorption from glomerulus. 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. Its molecular formula is $C_{27}H_{32}ClNO_{10}$ and the structural formula is:



Ertugliflozin L-pyroglutamic acid

**QUALITATIVE & QUANTITATIVE COMPOSITION**

Ertuget (Ertugliflozin) Tablets are available for oral administration as:

Ertuget Tablets 5mg
Each film-coated tablet contains:
Ertugliflozin L-pyroglutamic acid equivalent to Ertugliflozin…5mg

Ertuget Tablets 15mg
Each film-coated tablet contains:
Ertugliflozin L-pyroglutamic acid equivalent to Ertugliflozin…15mg

**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 a potent, selective, and reversible 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.

**Pharmacokinetics**

*Absorption*

Following single-dose oral administration of 5mg and 15mg of Ertugliflozin, peak plasma concentrations (median $T_{max}$) of Ertugliflozin occur at 1-hour post dose under fasted conditions. Plasma $C_{max}$ and AUC of Ertugliflozin increase in a dose-proportional manner following single doses from 0.5mg (0.1 times the lowest recommended dose) to 300mg (20 times the highest recommended dose) and following multiple doses from 1mg (0.2 times the lowest recommended dose) to 100mg (6.7 times the highest recommended dose). The absolute oral bioavailability of Ertugliflozin following administration of a 15mg dose is approximately 100%.
Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

*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.

*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%).

*Elimination*

The mean systemic plasma clearance following an intravenous 100µg 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. 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.

**Special populations**

*Patients with Renal Impairment*

In patients with type 2 diabetes mellitus and mild, moderate, or severe renal impairment, 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. The 24-hour urinary glucose excretion declined with increasing severity of 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.

**THERAPEUTIC INDICATIONS**

Ertuget (Ertugliflozin) is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control:

- As monotherapy in patients for whom the use of metformin HCl is considered inappropriate due to intolerance or contraindications.
- In addition to other medicinal products for the treatment of diabetes.

**DOSAGE & ADMINISTRATION**

The recommended starting dose of Ertuget (Ertugliflozin) Tablets is 5mg once daily, taken in the morning, with or without food. In patients tolerating Ertuget (Ertugliflozin) 5mg once daily, the dose may be increased to a maximum recommended dose of 15mg once daily if additional glycemic control is needed.
In patients with volume depletion, correcting this condition prior to initiation of Ertuget (Ertugliflozin) is recommended.
When Ertuget (Ertugliflozin) Tablets are used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

*Missed dose*

If a dose is missed, it should be taken as soon as the patient remembers. Patients should not take two doses of Ertuget (Ertugliflozin) Tablets on the same day.

**Special populations**

*Renal impairment*

Assessment of renal function is recommended prior to initiation of Ertuget (Ertugliflozin) and periodically thereafter. Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) of 30 mL/minute/1.73m$^2$ to less than 60 mL/minute/1.73m$^2$.

*Hepatic Impairment*

No dose adjustment of Ertuget (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.

*Pediatric population*

The safety and efficacy of Ertuget (Ertugliflozin) in children under 18 years of age have not been established.

**ADVERSE REACTIONS**

The following adverse reactions have been reported with the use of Ertugliflozin therapy:

*Very common*

Vulvovaginal mycotic infection and other female genital mycotic infections.

*Common*

Balanitis candida, other male genital mycotic infections, hypoglycemia, volume depletion, increased urination, vulvovaginal pruritus, thirst, serum lipids changed, hemoglobin increased and bun increased.

*Uncommon*

Dysuria, blood creatinine increased and glomerular filtration rate decreased.

*Rare*

Diabetic ketoacidosis, hypotension, acute kidney injury, impairment in renal function, urosepsis, pyelonephritis, lower limb amputation, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (fournier's gangrene), increases in low-density lipoprotein cholesterol (LDL-C) and necrotizing fasciitis of the perineum (fournier's gangrene).

**"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"**

**CONTRAINDICATIONS**

Ertugliflozin is contraindicated in:

- Patients with hypersensitivity to Ertugliflozin or to any of the excipient of the product.
- Patients with Severe renal impairment, end-stage renal disease (ESRD) or on dialysis.

**PRECAUTIONS**

*General*

Ertugliflozin should not be used in patients with type 1 diabetes mellitus.

*Hypotension / Volume depletion*

Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Ertugliflozin particularly in patients with impaired renal function (eGFR less than 60 ml/min/1.73m$^2$ or CrCl less than 60 ml/min), elderly patients (≥ 65 years), patients on diuretics, or patients on antihypertensive therapy with a history of hypotension. Monitor for signs and symptoms after initiating therapy.
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 Ertugliflozin. Temporary interruption of treatment with Ertugliflozin should be considered until the fluid loss is corrected

*Ketoacidosis*

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors.
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 250mg/dL. If ketoacidosis is suspected. Ertugliflozin should be discontinued, patient should be evaluated, and prompt treatment should be instituted.

Before initiating, consider factors in the patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing Ertugliflozin for at least 4 days prior to surgery.
Patients who may be at higher risk of ketoacidosis, patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery, or alcohol abuse, SGLT2 inhibitors should be used with caution in these patients.

*Lower Limb Amputation*
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. Monitor patients receiving Ertugliflozin for signs and symptoms of infection such as lower-extremity skin ulcer, infection, new pain or tenderness, osteomyelitis or gangrene, and discontinue Ertugliflozin if these complications occur.

*Acute Kidney Injury and Impairment in Renal Function*
Ertugliflozin causes intravascular volume contraction and can cause renal impairment. There have been reports of acute kidney injury some requiring hospitalization and dialysis in patients receiving SGLT2 inhibitors.
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.

*Urosepsis and Pyelonephritis*
There have been 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.

*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 in patients with diabetes mellitus receiving SGLT2 inhibitors.
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.

*Elderly patients*
Elderly patients may be at an increased risk of volume depletion. Patients 65 years and older treated with Ertugliflozin had a higher incidence of adverse reactions related to volume depletion compared to younger patients. Ertugliflozin is expected to have diminished efficacy in elderly patients with renal impairment.

*Increases in Low-Density Lipoprotein Cholesterol (LDL-C)*
Dose-related increases in LDL-C can occur with Ertugliflozin. Monitor and treat as appropriate.

*Lactose*
This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

*Effects on ability to drive and use machines*
Ertugliflozin has no or negligible influence on the ability to drive or use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported.

**Pregnancy**
Ertugliflozin is not recommended during the second and third trimesters of pregnancy. Ertugliflozin should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

**Nursing Mothers**
Ertugliflozin is not recommended while breastfeeding.

**DRUG INTERACTIONS**
*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.

*Diuretics*
Ertugliflozin may add to the diuretic effect of 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.

**OVERDOSAGE**
Ertugliflozin did not show any toxicity at single oral doses up to 300mg and multiple doses up to 100mg 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 hemodialysis has not been studied.

**STORAGE**
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the recommended conditions.

**HOW SUPPLIED**
Ertuget (Ertugliflozin) Tablets 5mg are available in blister pack of 14's.
Ertuget (Ertugliflozin) Tablets 15mg are available in blister pack of 14's

***Keep out of reach of children.***

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

**Please read the contents carefully before use.**
**This package insert is continually updated from time to time.**

Manufactured by:
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