02-09-0405

# Ertuvia-S

## (Ertugliflozin and Sitagliptin) Tablets

**Product Specifications: Innovator**
**Ertuvia-S 5mg/100mg Tablets:**
Each film coated tablet contains: Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin ..... 5 mg
Sitagliptin phosphate monohydrate U.S.P. eq. to Sitagliptin ..... 100 mg
**Ertuvia-S 15mg/100mg Tablets:**
Each film coated tablet contains: Ertugliflozin L-pyroglutamic acid eq. to Ertugliflozin ..... 15 mg
Sitagliptin phosphate monohydrate U.S.P. eq. to Sitagliptin ..... 100 mg

**DESCRIPTION**
Ertuvia-S (ertugliflozin and sitagliptin) tablet for oral use contains ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor, and sitagliptin phosphate, a DPP-4 inhibitor.
**Ertugliflozin:** 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 $C_{27}H_{33}ClNO_{10}$ and the molecular weight is 566.00.
**Sitagliptin:** Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The empirical formula is $C_{16}H_{15}F_6N_5O{\bullet}H_3PO_4{\bullet}H_2O$ and the molecular weight is 523.32.

**CLINICAL PARTICULARS**
**Therapeutic indications**
Ertuvia-S (ertugliflozin and sitagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.
**Limitations of Use**
Ertuvia-S (ertugliflozin and sitagliptin) is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
Ertugliflozin / Sitagliptin has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ertugliflozin / sitagliptin**.**
**Posology and method of administration**
Recommended Dosage
- The recommended starting dose of Ertuvia-S is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating Ertuvia-S (ertugliflozin and sitagliptin), the dose may be increased to a maximum recommended dose of 15 mg ertugliflozin/100 mg sitagliptin, once daily, if additional glycemic control is needed.
- For patients treated with ertugliflozin who are being switched to Ertuvia-S (ertugliflozin and sitagliptin), the dose of ertugliflozin can be maintained.
- In patients with volume depletion, correct this condition prior to initiation of Ertuvia-S (ertugliflozin and sitagliptin).

Recommended Dosage in Patients with Renal Impairment
- Assess renal function prior to initiation of Ertuvia-S (ertugliflozin and sitagliptin) and periodically thereafter.
- Use of Ertuvia-S (ertugliflozin and sitagliptin) is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m**²**.
- Initiation of Ertuvia-S (ertugliflozin and sitagliptin) is not recommended in patients with an eGFR of 30 mL/min/1.73 m$^2$ to less than 60 mL/min/1.73 m**²**.
- Continued use of Ertuvia-S (ertugliflozin and sitagliptin) is not recommended when eGFR is persistently between 30 and less than 60 mL/min/1.73 m**²**.
- No dose adjustment is needed in patients with mild renal impairment.

**Contraindication**
- Severe renal impairment, end-stage renal disease (ESRD), or dialysis**.**
- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.
- History of a serious hypersensitivity reaction to ertugliflozin.

**WARNINGS AND PRECAUTIONS**
Pancreatitis: There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin, a component of Ertugliflozin / Sitagliptin tablets. After initiation of Ertugliflozin / Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Ertugliflozin / Sitagliptin should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Ertugliflozin / Sitagliptin**.**
Hypotension: Ertugliflozin, a component of Ertugliflozin / Sitagliptin tablets, causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Ertugliflozin / Sitagliptin 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 / Sitagliptin, 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 medicines containing 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 medicines containing SGLT2 inhibitors. Ertugliflozin / Sitagliptin is not indicated for the treatment of patients with type 1 diabetes mellitus.
Patients treated with Ertugliflozin / Sitagliptin 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 / Sitagliptin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Ertugliflozin / Sitagliptin 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 / Sitagliptin, 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 / Sitagliptin for at least 4 days prior to surgery.
Consider monitoring for ketoacidosis and temporarily discontinuing Ertugliflozin / Sitagliptin 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 / Sitagliptin.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Ertugliflozin / Sitagliptin and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury and Impairment in Renal Function: Ertugliflozin / Sitagliptin 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 / Sitagliptin, 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 / Sitagliptin 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 / Sitagliptin promptly and institute treatment.
Ertugliflozin, a component of Ertugliflozin / Sitagliptin tablets, 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 to these changes. Renal function abnormalities can occur after initiating Ertugliflozin / Sitagliptin. Renal function should be evaluated prior to initiating Ertugliflozin / Sitagliptin and periodically thereafter. Use of Ertugliflozin / Sitagliptin 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**.
There have been post-marketing reports with sitagliptin of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal insufficiency has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating Ertugliflozin / Sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function. Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.
Urosepsis and Pyelonephritis: There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving medicines containing SGLT2 inhibitors. Cases of pyelonephritis also have been reported in ertugliflozin-treated patients in clinical trials. Treatment with medicines containing 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 / Sitagliptin, 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 / Sitagliptin for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue Ertugliflozin / Sitagliptin if these complications occur.
Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of Ertugliflozin / Sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Ertugliflozin / Sitagliptin**.**
Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Ertugliflozin, a component of Ertugliflozin / Sitagliptin tablets, may increase the risk of hypoglycemia when used in combination with insulin and/or an insulin secretagogue**.** When sitagliptin, a component of Ertugliflozin / Sitagliptin tablets, was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Ertugliflozin / Sitagliptin**.**
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 / Sitagliptin 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 / Sitagliptin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.
Genital Mycotic Infections: Ertugliflozin, a component of Ertugliflozin / Sitagliptin tablets, 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.
Hypersensitivity Reactions
There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, a component of Ertugliflozin / Sitagliptin tablets. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Ertugliflozin / Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes.
Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Ertugliflozin / Sitagliptin**.**
Increases in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in LDL-C can occur with ertugliflozin, a component of Ertugliflozin / Sitagliptin tablets**.** Monitor and treat as appropriate.
Severe and Disabling Arthralgia
There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years.
Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor.
Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
Bullous Pemphigoid:
Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP- 4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Ertugliflozin / Sitagliptin. If bullous pemphigoid is suspected, Ertugliflozin / Sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.
Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Ertugliflozin / Sitagliptin.
**USE IN SPECIFIC POPULATIONS**
Pregnancy: Based on animal data showing adverse renal effects, from ertugliflozin, Ertugliflozin / Sitagliptin is not recommended during the second and third trimesters of pregnancy.
The limited available data with ertugliflozin and sitagliptin use during pregnancy 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

Lactation: There is no information regarding the presence of Ertugliflozin / Sitagliptin, in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin and sitagliptin are present in the milk of lactating rats. Because of the potential for serious adverse reactions in a breastfed infant, advise women that the use of Ertugliflozin / Sitagliptin is not recommended while breastfeeding.
Pediatric Use: Safety and effectiveness of Ertugliflozin / Sitagliptin in pediatric patients under 18 years of age have not been established.
Geriatric Use: No dosage adjustment of Ertugliflozin / Sitagliptin is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and sitagliptin is known to be substantially excreted by the kidneys, renal function should be assessed more frequently in elderly patients. Ertugliflozin / Sitagliptin is expected to have diminished efficacy in elderly patients with renal impairment
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 / Sitagliptin is not recommended in this population.
Ertugliflozin / Sitagliptin is contraindicated in patients with severe renal impairment, ESRD, or receiving dialysis. Ertugliflozin / Sitagliptin 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 / Sitagliptin is necessary in patients with mild or moderate hepatic impairment. Ertugliflozin / Sitagliptin 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 / Sitagliptin 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 / Sitagliptin**.**
Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking medicines containing an SGLT2 inhibitor 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 medicines containing an SGLT2 inhibitor.
Use alternative methods to monitor glycemic control.
Digoxin: There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration ($C_{max}$, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Ertugliflozin / Sitagliptin is recommended.

**Adverse Reactions**

The following important adverse reactions related to Ertugliflozin / Sitagliptin are described below and elsewhere in the labeling:
Pancreatitis; Hypotension; Ketoacidosis; Acute Kidney Injury and Impairment in Renal Function; Urosepsis and Pyelonephritis; Lower Limb Amputation; Heart Failure; Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues; Necrotizing Fasciitis of the Perineum (Fournier's gangrene); Genital Mycotic Infections; Hypersensitivity Reactions; Increases in Low-Density Lipoprotein (LDL-C); Severe and Disabling Arthralgia; Bullous Pemphigoid
Post-Marketing Experience
Sitagliptin: Additional adverse reactions have been identified during post-approval use of sitagliptin, a component of Ertugliflozin / Sitagliptin tablets, as monotherapy and/or in combination with other antihyperglycemic agents.
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.
Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous emphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; rhabdomyolysis.
Ertugliflozin: Additional adverse reactions have been identified during post-approval use. 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 / Sitagliptin tablets, employ the usual supportive measures as dictated by the patient's clinical status.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Ertugliflozin / Sitagliptin tablets combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: ertugliflozin, a SGLT2 inhibitor, and sitagliptin, a DPP-4 inhibitor.
Ertugliflozin: 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.
Sitagliptin: Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

**Pharmacodynamics**

Ertugliflozin
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.
Cardiac Electrophysiology: At 6.7 times the therapeutic exposures with maximum recommended dose, ertugliflozin does not prolong QTc to any clinically relevant extent.
Sitagliptin
General: In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of sitagliptin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.
Cardiac Electrophysiology: At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo corrected mean change in QTc from baseline was observed at 3 hours post-dose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

**Pharmacokinetics**

Absorption: Administration of Ertugliflozin / Sitagliptin tablets with food decreased ertugliflozin $C_{max}$ by 29% and had no meaningful effect on ertugliflozin $AUC_{inf}$, and on sitagliptin $AUC_{inf}$ and $C_{max}$**.**
Distribution
Ertugliflozin: 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.
Sitagliptin: The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 L. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).
Elimination
Metabolism
*Ertugliflozin:* 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%).
*Sitagliptin:* Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a [$^{14}$C] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin.
Excretion
*Ertugliflozin:* 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.
*Sitagliptin:* Following administration of an oral [$^{14}$C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.
Specific Populations
Patients with Renal Impairment
*Ertugliflozin:* In a clinical trial; 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 plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.
*Sitagliptin:* An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 $m^2$, and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.
Patients with Hepatic Impairment
*Ertugliflozin:* Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. 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.
*Sitagliptin:* In patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), mean AUC and $C_{max}$ of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. No dosage adjustment for sitagliptin is necessary for patients with mild or moderate hepatic insufficiency. There is no clinical experience in patients with severe hepatic insufficiency.
Effects of Age, Body Weight/ Body Mass Index (BMI), Gender, and Race
*Ertugliflozin:* Based on a population pharmacokinetics (PK) analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the PK of ertugliflozin.
*Sitagliptin:* Based on a population PK analysis or a composite analysis of available PK data, BMI, gender, and race do not have a clinically meaningful effect on the PK of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the PK of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

**HOW SUPPLIED**

Ertuvia-S 5mg/100mg Tablets: Pack of 14 Tablets
Ertuvia-S 15mg/100mg 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:*
FEROZSONS LABORATORIES LIMITED
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