EGLARO®-S

(Ertugliflozin + Sitagliptin)

اِگلیرو۔ایس

COMPOSITION
Eglaro-S 5/100mg:
Each film coated tablet contains:
Ertugliflozin L-Pyroglutamic Acid eq to Ertugliflozin 5mg
Sitagliptin (as phosphate monohydrate USP) 100mg
Eglaro-S 15/100mg:
Each film coated tablet contains:
Ertugliflozin L-Pyroglutamic Acid eq to Ertugliflozin 15mg
Sitagliptin (as phosphate monohydrate USP) 100mg
(As per innovator's specs.)

DESCRIPTION
Eglaro-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-(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.

Sitagliptin
Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate.

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32.

CLINICAL PHARMACOLOGY

Mechanism of Action
Eglaro-S
Eglaro-S 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. 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.

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 insulin 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 a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes mellitus.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology
In a randomized, placebo controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. 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 postdose 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.

In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Pharmacokinetics

Ertugliflozin
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.

Sitagliptin
The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady state compared to the first dose. The intra subject and inter subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

Eglaro-S
The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and sitagliptin when administered are comparable to those reported for the individual tablets. Administration of ertugliflozin and sitagliptin with food decreased ertugliflozin Cmax by 29% and had no meaningful effect on ertugliflozin AUCinf, and on sitagliptin AUCinf and Cmax.

Ertugliflozin
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations of ertugliflozin occur at 1 hour postdose (median Tmax) 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%.

Effect of Food
Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin Cmax by 29% and prolongs Tmax 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.

Sitagliptin
The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

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%).

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 [14C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

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 [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.

Sitagliptin
Following administration of an oral [14C]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 t1/2 following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Pharmacokinetics in special populations
Patients with renal impairment

Eglaro-S
Studies characterizing the pharmacokinetics of ertugliflozin and sitagliptin after administration in renally impaired patients have not been performed.

Ertugliflozin
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 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.

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 m2, 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. 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.

Sitagliptin
In patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. 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 (Child Pugh score >9).

Effects of Age, Body Weight/ Body Mass Index (BMI), Gender, and Race

Ertugliflozin
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

Sitagliptin
Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics 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 pharmacokinetics 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.

INDICATIONS
Eglaro-S is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

Recommended Dosage
The recommended starting dose of Eglaro-S is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food.

For patients treated with ertugliflozin who are being switched to Eglaro-S, the dose of ertugliflozin can be maintained.

For additional glycemic control, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily in patients tolerating Eglaro-S.

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

Dosage adjustment

Renal impairment
Assessment of renal function is recommended prior to initiation of Eglaro-S and periodically
Thereafter. Initiation of Eglaro-S is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m2 or CrCl less than 45 mL/min.

In patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m2, Eglaro-S should be initiated at 5 mg/100 mg and up-titrated to 15 mg/100 mg as needed for glycaemic control.

Because the glycaemic lowering efficacy of ertugliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other antihyperglycaemic agents should be considered.

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

The fixed-dose combination of ertugliflozin and sitagliptin should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as there is no clinical data to support effectiveness in these patients.

Hepatic impairment
No dose adjustment of Eglaro-S is necessary in patients with mild or moderate hepatic impairment.

Eglaro-S 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 Eglaro-S 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. Renal function and risk of volume depletion should be taken into account.

CONTRAINDICATIONS
• Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

• Use of Eglaro-S is contraindicated in patients with severe renal impairment (<30 mL/min/1.73 m2), end-stage renal disease (ESRD) or on dialysis.

• Hypersensitivity to sitagliptin, ertugliflozin, or any excipient, in Eglaro-S.

WARNING AND PRECAUTIONS

Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin, a component of Eglaro-S. After initiation of Eglaro-S, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Eglaro-S 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 Eglaro-S.

Ketoacidosis
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving medicines containing 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. Eglaro-S is not indicated for the treatment of patients with type 1 diabetes mellitus.
Patients treated with ertugliflozin and 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 and sitagliptin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, ertugliflozin and 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 and 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 and sitagliptin for at least 4 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing ertugliflozin and 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 and sitagliptin.
Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue ertugliflozin and sitagliptin 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 and 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 and sitagliptin for signs and

symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue ertugliflozin and sitagliptin if these complications occur.

Acute Renal Failure
There have been postmarketing 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 and 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.

Volume Depletion
Ertugliflozin and sitagliptin 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 and sitagliptin. 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 and sitagliptin 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 and sitagliptin. 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 medicines containing SGLT2 inhibitors. 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.

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 and 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 and sitagliptin.

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. When sitagliptin, was used in combination with a sulfonylurea or with insulin, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ertugliflozin and 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 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 and 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 and sitagliptin, 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.

Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. 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 and 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 and sitagliptin.

Severe and Disabling Arthralgia
There have been postmarketing 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
Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP4 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 and sitagliptin. If bullous pemphigoid is suspected, ertugliflozin and sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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 from placebo- and active comparator-controlled clinical trials and post-marketing experience

System Organ Class Frequency	**Adverse Reaction**
Infections and infestations	
Very common	Vulvovaginal mycotic infection and other female genital mycotic infections Urinary tract infections
Common	Balanitis candida and other male genital mycotic infections
Not known	Necrotising fasciitis of the perineum (Fournier's gangrene)
Blood and lymphatic system disorders	
Rare	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity reactions including anaphylactic responses
Metabolism and nutrition disorders	
Common	Hypoglycaemia
Rare	Diabetic ketoacidosis
Nervous system disorders	
Common	Headache
Uncommon	Dizziness
Vascular disorders	
Common	Volume depletion
Gastrointestinal disorders	
Uncommon	Constipation
Not known	Vomiting
Not known	Acute pancreatitis
Not known	Fatal and non-fatal haemorrhagic and necrotizing pancreatitis
Skin and subcutaneous tissue disorders	
Uncommon	Pruritusa
Not known	Angioedema
Not known	Rash
Not known	Urticaria
Not known	Cutaneous vasculitis
Not known	Exfoliative skin conditions including Stevens-Johnson syndrome
Not known	Bullous pemphigoida
Musculoskeletal and connective tissue disorders	
Not known	Arthralgia
Not known	Myalgia
Not known	Back pain
Not known	Arthropathy
Renal and urinary disorders	
Common	Increased urination
Uncommon	Dysuria, Blood creatinine increased/Glomerular filtration rate decreased
Not known	Impaired renal function
Not known	Acute renal failure
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
Pharmacokinetic drug interaction studies with Ertugliflozin and sitagliptin combination have not been performed; however, such studies have been conducted with ertugliflozin and sitagliptin, the individual active substances of Ertugliflozin and sitagliptin.

Ertugliflozin

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 and sitagliptin.

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.

Sitagliptin
Pharmacokinetic interactions

Effects of other medicinal products on sitagliptin
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. In vitro studies indicate that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8.

Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD.

Interaction studies conducted in patients with type 2 diabetes or healthy volunteers suggest that metformin and ciclosporin had no clinically relevant effect on the pharmacokinetics of sitagliptin.

Effects of sitagliptin on other medicinal products
In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives.

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11% and the plasma Cmax on average by 18%. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

USE IN SPECIAL POPULATIONS
Pregnancy
There are no data from the use of ertugliflozin and sitagliptin in pregnant women. 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, ertugliflozin and sitagliptin should not be used during pregnancy.

Breast-feeding
There is no information regarding the presence of ertugliflozin and sitagliptin or its individual components in human milk, the effects on the breast-fed infant, or the effects on milk production. No studies in lactating animals have been conducted with the combined components of Eglaro-S. Ertugliflozin and sitagliptin are present in the milk of lactating rats. Ertugliflozin caused effects in the offspring of lactating rats.

Pharmacologically mediated effects were observed in juvenile rats treated with ertugliflozin. 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. Eglaro-S should not be used during breast-feeding.

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

Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m2 or CrCl less than 45 mL/min.

In patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m2, Eglaro-S should be initiated at 5 mg/100 mg and up-titrated to 15 mg/100 mg as needed for glycaemic control.

Because the glycaemic lowering efficacy of ertugliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other antihyperglycaemic agents should be considered.

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

The fixed-dose combination of ertugliflozin and sitagliptin should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as there is no clinical data to support effectiveness in these patients.

Hepatic impairment
Eglaro-S has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

Elderly (≥ 65 years old)
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. Renal function and risk of volume depletion should be taken into account.

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

OVER DOSAGE
In the event of an overdose with Eglaro-S, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring including obtaining an electrocardiogram, and institute supportive treatment) as dictated by the patient's clinical status.

Ertugliflozin
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. Removal of ertugliflozin by haemodialysis has not been studied.

Sitagliptin
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase 1 multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

PRESENTATION
Eglaro S 5/100mg : Pack of 14 tablets.
Eglaro S 15/100mg : Pack of 14 tablets.

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

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

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