Trevia® R2

[Ertugliflozin+Sitagliptin]

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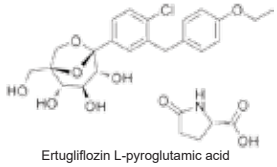
5mg + 100mg & 15mg + 100mg
Tablets

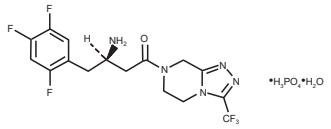
DESCRIPTION
Trevia R2 Tablets for oral use contains Ertugliflozin L-pyroglutamic acid, a SGLT2 inhibitor and Sitagliptin phosphate, a DPP-4 inhibitor.

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

Sitagliptin is an inhibitor of the enzyme dipeptidylpeptidase-4 (DPP-4), an enzyme responsible for the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1). It is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl] -5,6,7,8-tetrahydro (trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. Its molecular formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the structural formula is:



Sitagliptin phosphate monohydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION
Trevia R2 (Ertugliflozin + Sitagliptin) is available for oral administration as:

Trevia R2 Tablets 5mg + 100mg
Each film-coated tablet contains:
Ertugliflozin L-pyroglutamic acid equivalent to Ertugliflozin…5mg
Sitagliptin phosphate (as monohydrate) USP equivalent to Sitagliptin…100mg

Trevia R2 Tablets 15mg + 100mg
Each film-coated tablet contains:
Ertugliflozin L-pyroglutamic acid equivalent to Ertugliflozin…15mg
Sitagliptin phosphate (as monohydrate) USP equivalent to Sitagliptin…100mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ertugliflozin
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. Ertugliflozin also causes an osmotic diuresis, which may result in increase of urinary glucose excretion.

Sitagliptin
Sitagliptin improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels.

Pharmacokinetics
Absorption
Ertugliflozin
After oral administration of 5mg and 15mg of Ertugliflozin, peak plasma concentrations of Ertugliflozin occur at 1 hour under fasted conditions. Plasma C_{max} and AUC of Ertugliflozin increase in a dose-proportional manner following single doses from 0.5mg to 300mg and following multiple doses from 1mg to 100mg. The absolute oral bioavailability of Ertugliflozin following administration of a 15mg dose is approximately 100%.

Sitagliptin
The absolute bioavailability of Sitagliptin is approximately 87%. Because coadministration of a high fat meal with Sitagliptin had no effect on the pharmacokinetics.

Distribution
Ertugliflozin
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 100mg intravenous dose of Sitagliptin to healthy subjects is approximately 198L. The fraction of Sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism
Ertugliflozin
The major metabolic pathway for Ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides. CYP-mediated (oxidative) metabolism of Ertugliflozin is minimal (12%).

Sitagliptin
Following a [^{14}C] 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. Primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Excretion
Ertugliflozin
The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 16.6 hours. 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
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. Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Special Populations
Patients with Renal Impairment
Ertugliflozin
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.

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/1.73m^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 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.

Sitagliptin
In patients with moderate hepatic insufficiency, mean AUC and C_{max} of Sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100mg dose of Sitagliptin. No dosage adjustment for Sitagliptin is necessary for patients with mild or moderate hepatic insufficiency.

THERAPEUTIC INDICATIONS
Trevia R2 (Ertugliflozin + 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.

DOSAGE & ADMINISTRATION
Prior to Initiation of Trevia R2 (Ertugliflozin + Sitagliptin)
Assess renal function prior to initiation of Trevia R2 (Ertugliflozin + Sitagliptin) and as clinically indicated.
In patients with volume depletion, correct this condition before initiating Trevia R2 (Ertugliflozin + Sitagliptin).

Recommended dosage
The recommended starting dose of Trevia R2 (Ertugliflozin + Sitagliptin) is 5mg Ertugliflozin + 100mg Sitagliptin once daily, taken in the morning, with or without food. In patients tolerating Trevia R2 (Ertugliflozin + Sitagliptin), the dose may be increased to a maximum recommended dose of 15mg Ertugliflozin + 100mg Sitagliptin, once daily, if additional glycemic control is needed. For patients treated with Ertugliflozin who are being switched to Trevia R2 (Ertugliflozin + Sitagliptin), the dose of Ertugliflozin can be maintained.

Special Population
Patients with Renal Impairment
Use of Trevia R2 (Ertugliflozin + Sitagliptin) is contraindicated in patients with an eGFR less than 30mL/min/1.73m^2, end-stage renal disease (ESRD) or on dialysis. Initiation of Trevia R2 (Ertugliflozin + Sitagliptin) is not recommended in patients with an eGFR less than 45mL/min/1.73m^2.

Hepatic impairment
No dose adjustment of Trevia R2 (Ertugliflozin + Sitagliptin) is necessary in patients with mild or moderate hepatic impairment. Trevia R2 (Ertugliflozin + Sitagliptin) has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients.

Pediatric population
Safety and effectiveness of Trevia R2 (Ertugliflozin + Sitagliptin) in pediatric patients under 18 years of age have not been established.

Elderly
No dose adjustment is required based on age.

Concomitant use with insulin or an insulin secretagogue
Coadministration of Trevia R2 (Ertugliflozin + Sitagliptin) with insulin or an insulin secretagogue may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

ADVERSE REACTIONS
The following adverse reactions have bee reported with the use of Ertugliflozin + Sitagliptin:
Pancreatitis, hypotension, ketoacidosis, acute kidney injury, impairment in renal function, urosepsis, 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, severe and disabling arthralgia, bullous pemphigoid, upper respiratory tract infection, nasopharyngitis, urinary tract infections, vaginal pruritus, increased urination, back pain, weight decreased and headache.

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

CONTRAINDICATIONS
Ertugliflozin + Sitagliptin Tablet is contraindicated in patients with:
- Known hypersensitivity to Ertugliflozin, Sitagliptin and to any of the excipient of the product.
- Severe renal impairment, end-stage renal disease (ESRD) or on dialysis.

PRECAUTIONS
Pancreatitis
There have been postmarketing reports of acute pancreatitis in patients taking Sitagliptin. 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.

Hypotension
Ertugliflozin causes intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Ertugliflozin + Sitagliptin particularly in patients with impaired renal function (eGFR less than 60mL/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 patients with type 1 and type 2 diabetes mellitus receiving 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 250mg/dL. If ketoacidosis is suspected, Ertugliflozin + Sitagliptin should be discontinued.

Acute Renal Failure
There have been postmarketing reports of acute renal failure in patients taking Sitagliptin, sometimes requiring dialysis. Monitor renal function.

Urosepsis and Pyelonephritis
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
Before administration 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
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.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
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 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 allergic and hypersensitivity reactions in patients treated with Sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly discontinue Sitagliptin, assess for other potential causes, institute appropriate monitoring and treatment and initiate alternative treatment for diabetes.

Increases in LDL-C
Dose-related increases in LDL-C can occur with Ertugliflozin. Monitor and treat as appropriate.

Severe and Disabling Arthralgia
There have been severe and disabling arthralgia in patients taking DPP-4 inhibitors. Patients experienced relief of symptoms upon discontinuation of the medication. 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 DPP- inhibitor use. Inform 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.

Effects on ability to drive and use machines
Ertugliflozin + Sitagliptin 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 + Sitagliptin is not recommended during the second and third trimesters of pregnancy. Ertugliflozin + Sitagliptin should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers
Ertugliflozin + Sitagliptin is not recommended while breastfeeding.

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
Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Ertugliflozin + Sitagliptin is recommended.

OVERDOSAGE
In the event of an overdose, 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 300mg and multiple doses up to 100mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified.

Sitagliptin
Sitagliptin is modestly dialyzable. 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 dialyzable by peritoneal dialysis.

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

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

HOW SUPPLIED
Trevia R2 (Ertugliflozin + Sitagliptin) Tablets 5mg + 100mg are available in pack of 14's.

Trevia R2 (Ertugliflozin + Sitagliptin) Tablets 15mg + 100mg are available in 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:
Getz pharma (PVT) LIMITED
www.getzpharma.com
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