CARBOTRAP®

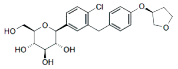
कार्बोट्राप

Empagliflozin Tablets 10 mg & 25 mg

DESCRIPTION:

CARBOTRAP tablets contain Empagliflozin, an orally-active inhibitor of the sodium glucose co-transporter 2 (SGLT2).

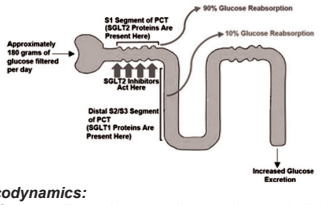
Its molecular formula is C23H27ClO7 and the molecular weight is 450.91. The structural formula is:



Each film-coated tablet (FCT) of CARBOTRAP contains 10 mg or 25 mg of Empagliflozin (free base).

CLINICAL PHARMACOLOGY:

Mechanism of action: Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.



Pharmacodynamics:

Urinary Glucose Excretion -In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of Empagliflozin (CARBOTRAP) and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg Empagliflozin and 78 grams per day with 25 mg Empagliflozin (CARBOTRAP) once daily. Data from single oral doses of Empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume -In a 5-day study, mean 24-hour urine volume increase from baseline was 341 ml on Day 1 and 135 ml on Day 5 of Empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology -In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of Empagliflozin 25 mg, Empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg Empagliflozin.

Pharmacokinetics:

Absorption -The pharmacokinetics of Empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of Empagliflozin were reached at 1.5 hours post-dose. Thereafter,plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and Cmax were 1870 nmol•h/L and 259 nmol/L, respectively, with 10 mg Empagliflozin once daily treatment, and 4740 nmol•h/L and 687 nmol/L, respectively, with 25 mg Empagliflozin once daily treatment. Systemic exposure of Empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin were similar, suggesting linear pharmacokinetics with respect to time. Administration of 25 mg Empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. The observed effect of food on Empagliflozin pharmacokinetics was not considered clinically relevant and Empagliflozin may be administered with or without food.

Distribution -The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism -No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates. Systemic exposure of each metabolite was less than 10% of total drug-related material. In vitro studies suggested that the primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases.

Elimination -The apparent terminal elimination half-life of Empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with Empagliflozin half-life. Following administration of an oral Empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Specific Populations:

Renal Impairment -In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of Empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of Empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of Empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of Empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of Empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Hepatic Impairment -In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of Empagliflozin increased by approximately 23%, 47%, and 75%, and Cmax increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. Effects of Age, Body Mass Index, Gender, and Race -Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of Empagliflozin.

Pediatric -Studies characterizing the pharmacokinetics of Empagliflozin in pediatric patients have not been performed.

INDICATIONS & USES:

CARBOTRAP is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use -CARBOTRAP is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE & ADMINISTRATION:

Recommended Dosage:

The recommended dose of CARBOTRAP is 10 mg once daily in the morning, taken with or without food. In patients tolerating CARBOTRAP, the dose may be increased to 25 mg.

In patients with volume depletion, correcting this condition prior to initiation of CARBOTRAP is recommended.

Patients with Renal Impairment - Assessment of renal function is recommended prior to initiation of CARBOTRAP and periodically thereafter.

CARBOTRAP should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.CARBOTRAP should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2.

CONTRAINDICATIONS:

- History of serious hypersensitivity reaction to Empagliflozin or any of the excipients in CARBOTRAP.
- Severe renal impairment, end-stage renal disease, or dialysis.

WARNINGS & PRECAUTIONS:

Hypotension -CARBOTRAP causes intravascular volume contraction. Symptomatic hypotension may occur after initiating CARBOTRAP particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating CARBOTRAP, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis - Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including Empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking Empagliflozin. CARBOTRAP is not indicated for the treatment of patients with type 1 diabetes mellitus. For patients who undergo scheduled surgery, consider temporarily discontinuing CARBOTRAP for at least 3 days prior to surgery.

Acute Kidney Injury and Impairment in Renal Function - CARBOTRAP 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, including Empagliflozin; some reports involved patients younger than 65 years of age. Before initiating CARBOTRAP 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 CARBOTRAP in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heatexposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue CARBOTRAP promptly and institute treatment. CARBOTRAP increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating CARBOTRAP. Renal function should be evaluated prior to initiation of CARBOTRAP and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFRbelow 60 mL/min/1.73 m^2. Use of CARBOTRAP is not recommended when eGFR is persistently less than 45mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis -There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including CARBOTRAP. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues - Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when CARBOTRAP is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with CARBOTRAP.

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 Empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with CARBOTRAP 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 CARBOTRAP, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections -CARBOTRAP increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions -There have been post-marketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with CARBOTRAP. If a hypersensitivity reaction occurs, discontinue CARBOTRAP; treat promptly per standard of care, and monitor until signs and symptoms resolve. CARBOTRAPis contraindicated in patients with a previous serious hypersensitivity reaction to Empagliflozin or any of the excipients in CARBOTRAP.

Increased Low-Density Lipoprotein Cholesterol (LDL-C) -Increases in LDL-C can occur with CARBOTRAP. Monitor and treat as appropriate.

ADVERSE REACTIONS:

The following important adverse reactions are described:

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

DRUG INTERACTIONS:

Diuretics– Co-administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues– Co-administration of Empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

Positive Urine Glucose Test - Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay -Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

OVERDOSE:

In the event of an overdose with CARBOTRAP employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of Empagliflozin by hemodialysis has not been studied.

DOSAGE FORMS & STRENGTHS:

CARBOTRAP tablets are available as:

- 10 mg FCT (Film Coated Tablets)
  Packaging: 20 Tablets X 5 Blisters
- 25 mg FCT (Film Coated Tablets)
  Packaging: 20 Tablets X 5 Blisters

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