

Dapazin

5mg & 10mg
Tablets
(Dapagliflozin) Tablets

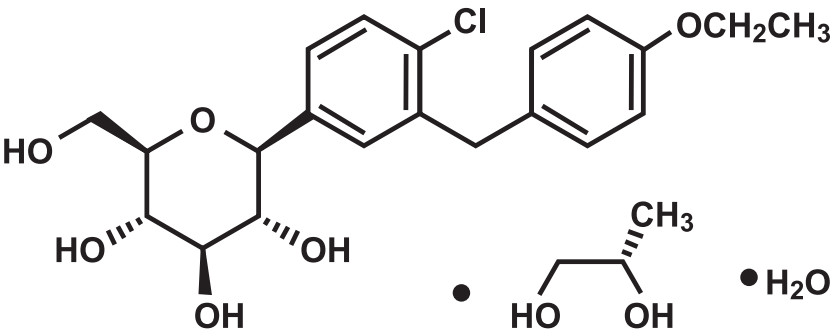
COMPOSITION

Each film coated tablet contains:
Dapagliflozin.....5mg
(As Dapagliflozin Propanediol Monohydrate).
As per Innovator’s Specifications.

Each film coated tablet contains:
Dapagliflozin.....10mg
(As Dapagliflozin Propanediol Monohydrate).
As per Innovator’s Specifications.

DESCRIPTION

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl) methyl]phenyl]-, (1S)-, compounded with (2S)-1,2 -propanediol, hydrate (1:1:1).
Its molecular formula is C₂₁H₂₅ClO₆.



CLINICAL PHARMACOLOGY

Mechanism of action:

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

PHARMACODYNAMICS

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Dapagliflozin dose of 10mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20mg. This urinary glucose excretion with dapagliflozin also results in increased urinary volume. Single dose up to 500mg of dapagliflozin is not associated with prolongation of QTc interval in healthy subjects.

PHARMACOKINETICS

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism

The metabolism of dapagliflozin is primarily mediated by

UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. The mean plasma terminal half-life (t_{1/2}) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10mg.

Specific Populations:

Renal Impairment

At steady-state (20mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes mellitus and mild, moderate and severe renal impairment was 42%, 80% and 90% lower, respectively, than in patients with type 2 diabetes mellitus with normal renal function. The impact of haemodialysis on dapagliflozin exposure is not known.

Hepatic Impairment

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Effects of Age, Gender, Race and Body Weight on Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

Pediatric

Pharmacokinetics in the pediatric population has not been studied.

THERAPEUTIC INDICATION

DAPAZIN (dapagliflozin) 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 hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.
- Dapagliflozin is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

ADVERSE REACTIONS

The most common adverse reactions associated with dapagliflozin (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections.

DOSAGE AND ADMINISTRATION
Table 1: Recommended Dosage

eGFR (mL/min/1.73 m ²)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5mg orally once daily. Dose can be increased to 10mg orally once daily for additional glycemic control. For all other indications, the recommended starting dose is 10mg orally once daily.
eGFR 25 to less than 45	10mg orally once daily.
eGFR less than 25	Initiation is not recommended, however, patients may continue 10mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema.
- Patients on dialysis.
- Dapagliflozin is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Dapagliflozin is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m². Dapagliflozin is likely to be ineffective in this setting based upon its mechanism of action.
- Dapagliflozin is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. Dapagliflozin is not expected to be effective in these populations.

WARNING AND PRECAUTIONS

Ketoacidosis in Patients with Diabetes Mellitus

Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue Dapagliflozin, evaluate and treat promptly. Before initiating Dapagliflozin, consider risk factors for ketoacidosis. Patients on Dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

Volume Depletion

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Patients with impaired renal function (eGFR less than 60mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Dapagliflozin in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including Dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections.

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

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

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, dose adjustments can be done for insulin or insulin secretagogues.

Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections.

DRUG INTERACTIONS

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-anhydroglucitol 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

There were no reports of overdose during the clinical development program for dapagliflozin.

STORAGE

- Store below 30°C
- Protect from heat, light and moisture.

PRESENTATION

DAPAZIN (dapagliflozin) tablets 5mg and 10mg are available as packs of 14’s.

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

Keep all medicines out of the reach of children.



Manufactured by :
Indus Pharma (Pvt.) Ltd.
65/27, Korangi Industrial Area,
Karachi-74900, Pakistan.

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