Dapxiga

(Dapagliflozin Tablets)

4000003105

Product Specifications: Innovator

Dapxiga Tablets 5 mg

Each film coated tablet contains:

Dapagliflozin propanediol monohydrate U.S.P. eq. to Dapagliflozin ..... 5 mg

Product contains Lactose

Dapxiga Tablets 10 mg

Each film coated tablet contains:

Dapagliflozin propanediol monohydrate U.S.P. eq. to Dapagliflozin ..... 10 mg

Product contains Lactose

DESCRIPTION

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98.

PHARMACEUTICAL FORM:

Film coated tablets

CLINICAL PARTICULARS

Therapeutic indications

Dapxiga (dapagliflozin) is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- 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.

Limitations of Use

- Dapxiga (dapagliflozin) is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Dapxiga (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 m^2. Dapxiga (dapagliflozin) is likely to be ineffective in this setting based upon its mechanism of action.
- Dapxiga (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. Dapxiga (dapagliflozin) is not expected to be effective in these populations.

Posology and method of administration

Prior to Initiation of Dapxiga (dapagliflozin)

Assess renal function prior to initiation of Dapxiga (dapagliflozin) therapy and then as clinically indicated.

Assess volume status and, if necessary, correct volume depletion prior to initiation of Dapxiga (dapagliflozin).

Recommended Dosage

In adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus, the recommended starting dosage of Dapxiga is 5 mg orally once daily to improve glycemic control. For additional glycemic control, the dosage can be increased to 10 mg orally once daily.

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

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 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* Dapxiga (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 m^2. Dapxiga (dapagliflozin) is likely to be ineffective in this setting based upon its mechanism of action.

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

Method of Administration

Dapagliflozin can be taken with or without food.

Contraindications

Dapagliflozin is contraindicated in:

- Patients with history of a serious hypersensitivity reaction to Dapagliflozin or to any excipient of the product such as anaphylactic reactions or angioedema.
- Patients on dialysis

Special warnings and precautions for use

Ketoacidosis in Patients with Diabetes Mellitus

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 sodium-glucose cotransporter 2 (SGLT2) inhibitors, including Dapagliflozin. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking Dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Dapagliflozin 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 Dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the post-marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the 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 Dapagliflozin, 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 Dapagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin 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 Dapagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin and seek medical attention immediately if signs and symptoms occur.

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 60 mL/min/1.73 m^2), 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. 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. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue.

Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Dapagliflozin.

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.

Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Interaction with other medicinal products

Table 2: Clinically Relevant Interactions with Dapagliflozin.

Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia may be increased when Dapagliflozin is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea)
Intervention	Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during Dapagliflozin initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on animal data showing adverse renal effects, Dapagliflozin is not recommended during the second and third trimesters of pregnancy. Limited data with Dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage.

Nursing Mothers

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin is not recommended while breastfeeding.

Pediatric

The safety and effectiveness of dapagliflozin for glycemic control in type 2 diabetes mellitus have not been established in pediatric patients less than 10 years of age.

The safety and effectiveness of dapagliflozin have not been established in pediatric patients to reduce the risk of:

- sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in patients with chronic kidney disease at risk of progression.
- cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in patients with heart failure.
- hospitalization for heart failure in patients with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.

Geriatric Use

No Dapagliflozin dosage change is recommended based on age. In clinical studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65.

Renal impairment
Efficacy and safety studies with Dapagliflozin did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2. Dapagliflozin is contraindicated in patients on dialysis.
Hepatic impairment
No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Undesirable effects

Clinical Trials Experience
Following adverse events were reported in clinical trials:
Female genital mycotic infections (including vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial), Nasopharyngitis, Urinary tract infections (urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis), Back pain, Increased urination (pollakiuria, polyuria, and urine output increased), Male genital mycotic infections (balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis), Nausea, Influenza, Dyslipidemia, Constipation, Discomfort with urination, Pain in extremity, Volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension), Hypoglycemia, Hypersensitivity reactions (angioedema, urticaria, hypersensitivity), Ketoacidosis in Patients with Diabetes Mellitus, Increases in Serum Creatinine, Hematocrit, Low-Density Lipoprotein Cholesterol, and Decreases in eGFR, Serum Bicarbonate.
Clinical Trial in Pediatric Patients with Type 2 Diabetes Mellitus
The dapagliflozin safety profile observed in a 26-week placebo-controlled clinical trial with a 26-week extension in 157 pediatric patients aged 10 years and older with type 2 diabetes mellitus was similar to that observed in adults.
Post-marketing Experience
Additional adverse reactions have been identified during post-approval use of dapagliflozin in patients with diabetes mellitus.
Ketoacidosis, Acute Kidney Injury, Urosepsis and Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), Rash

OVERDOSAGE

There were no reports of overdose during the clinical development program for Dapagliflozin.
It is reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.
Effects on ability to drive and use machines
Dapxiga has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01

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 thereby promotes urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

Pharmacodynamics properties

General
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 doses of 5 or 10 mg 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 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.
Cardiac Electrophysiology
Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

Pharmacokinetic properties

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 10 mg 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 50 mg [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. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of 10 mg.
Special population
Patients with renal impairment
At steady-state (20 mg 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%, 100%, and 200% higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. There was no meaningful difference in exposure between patients with chronic kidney disease with and without type 2 diabetes. 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 hemodialysis on dapagliflozin exposure is not known.
Patients with 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 10 mg 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.

HOW SUPPLIED

Dapxiga Tablet 5 mg:	Pack of 10 Tablets
Dapxiga Tablet 10 mg:	Pack of 10 Tablets

STORAGE

Do not store above 30°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from heat, light and moisture.
Keep all medicines out of the 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:
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