Dapwiz®
(DAPAGLIFLOZIN)

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COMPOSITION
Dapwiz 5mg Tablet:
Each film coated tablet contains:
Dapagliflozin propanediol monohydrate equivalent to 5mg Dapagliflozin.
(As per innovator's specs.)

Dapwiz 10mg Tablet:
Each film coated tablet contains:
Dapagliflozin propanediol monohydrate equivalent to 10mg Dapagliflozin.
(As per innovator's specs.)

DESCRIPTION
Dapwiz contains Dapagliflozin which is a Sodium-glucose cotransporter 2 (SGLT2) inhibitor. It 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). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the molecular weight is 502.98.

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. 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.

Pharmacodynamics
Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks result in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion may be observed at the Dapagliflozin daily dose of 20 mg. This urinary glucose excretion with Dapagliflozin also results in increases in urinary volume.

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 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 accounts 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 [14C]-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 (t½) for Dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.

Pharmacokinetics in special populations

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) have geometric mean systemic exposures of Dapagliflozin that are 45%, 2.04fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of Dapagliflozin in patients with type 2 diabetes mellitus with renal impairment does 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 and mild, moderate, and severe renal impairment is 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on Dapagliflozin exposure is not known.

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

Elderly
The pharmacokinetics of Dapagliflozin are not different in elderly.

Pediatric
No data is available on the pharmacokinetics in the pediatric population.

INDICATIONS

Type 2 Diabetes Mellitus
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.

Heart Failure
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.

When diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control.

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

DOSAGE AND ADMINISTRATION

Prior to Initiation of Dapagliflozin
Assess renal function prior to initiation of Dapagliflozin therapy and then as clinically indicated. In patients with volume depletion, correct this condition prior to initiation of Dapagliflozin.

Type 2 Diabetes Mellitus
To improve glycemic control, the recommended starting dose of Dapagliflozin is 5 mg orally once daily, taken in the morning, with or without food. In patients tolerating Dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.
To reduce the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus and established CVD or multiple CV risk factors, the recommended dose of Dapagliflozin is 10 mg orally once daily.

Heart Failure
The recommended dose of Dapagliflozin is 10 mg orally once daily.

Adult dosage
The recommended starting dose of Dapagliflozin is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Dapagliflozin, 5 mg once daily who require additional glycemic
control, the dose can be increased to 10 mg once daily.
In patients with volume depletion, correcting this condition prior to initiation of Dapagliflozin is recommended.

Dosage adjustment in special populations

Renal Impairment

Treatment/ Patient population	Recommended Dosage based on eGFR (mL/min/1.73 m^2, CKD-EPI)			
	45 or above	30 to less than 45	less than 30	ESRD/Dialysis
Use for glycemic control in patients with T2DM	No dose adjustment	Not recommended	Contraindicated	
To reduce the risk hHF in patients with T2DM, with CVD or multiple CV risk factors	No dose adjustment	Insufficient data to support a dosing recommendation.		Contraindicated
To reduce the risk of CV death and hHF in patients with HFrEF, with or without T2DM	No dose adjustment		Insufficient data to support a dosing recommendation.	Contraindicated

eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration equation, T2DM: Type 2 diabetes mellitus, hHF: hospitalization for heart failure, HFrEF: Heart failure with reduced ejection fraction, CVD: Cardiovascular disease, CV: Cardiovascular, ESRD: End Stage Renal Disease

Hepatic impairment
No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

Elderly (≥ 65 years)
No dose adjustment is recommended based on age.

Pediatric population
The safety and efficacy of Dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Administration requirements
Dapagliflozin can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

CONTRAINDICATIONS
- History of a serious hypersensitivity reaction to Dapagliflozin
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease (ESRD), or patients on dialysis

WARNING AND PRECAUTIONS

Lower Limb amputation
An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

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 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.

Diabetic Ketoacidosis
Ketoacidosis, a serious life-threatening condition may occur requiring urgent hospitalization in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose co-transporter 2 (SGLT2) inhibitors, including Dapagliflozin. Fatality due to ketoacidosis may also occur 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.
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. In patients treated with Dapagliflozin consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

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 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.

Urosepsis and Pyelonephritis
Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization may occur 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
Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can 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.

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

Effects on ability to drive and use machines
Dapagliflozin 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.

ADVERSE REACTIONS

Infections and infestations
Common: Vulvovaginitis, balanitis and related genital infections, Urinary tract infection (including pyelonephritis and urosepsis)
Uncommon: Fungal infection
Metabolism and nutrition disorders
Very common: Hypoglycaemia (when used with sulphonylurea or insulin)
Uncommon: Volume depletion, Thirst
Rare: Diabetic ketoacidosis
Nervous system disorders
Common: Dizziness
Gastrointestinal disorders
Uncommon: Constipation, Dry mouth
Skin and subcutaneous tissue disorders
Common: Rash
Musculoskeletal and connective tissue disorders
Common: Back pain
Not Known: Fracture of Bone
Renal and urinary disorders
Common: Dysuria, Polyuria
Uncommon: Nocturia, Renal impairment
Reproductive system and breast disorders
Uncommon: Vulvovaginal pruritus, Pruritus genital
Investigations
Common: Haematocrit increased, Creatinine renal clearance decreased, Dyslipidaemia
Uncommon: Blood creatinine increased, Blood urea increased, Weight decreased

DRUG INTERACTIONS

ACE inhibitors and Antidiabetic agents
Concurrent use of ACE INHIBITORS and ANTIDIABETIC AGENTS may result in increased risk of hypoglycemia.
Flouroquinolones
Concurrent use of flouroquinolones and antidiabetic agents may result in changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.
Somatostatin Analogues
Concurrent use of antidiabetic agents and somatostatin analogues may result in impaired glucose regulation.
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.

USE IN SPECIAL POPULATIONS

Pregnancy
There is no data for the use of dapagliflozin in pregnant women. The use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.
When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Nursing mother
It is not known whether Dapagliflozin is excreted in human milk. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Pediatrics
Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.

Elderly
No Dapagliflozin dosage change is recommended based on age.

Renal impairment
See dose adjustment in special populations

Hepatic impairment
See dose adjustment in special populations

OVER DOSAGE
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. No data is available on the removal of Dapagliflozin by haemodialysis.

PRESENTATION
Dapwiz 5mg : Pack of 10 tablets.
Dapwiz 10mg : Pack of 10 tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the sight & 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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