For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Prescribing Information

1. Generic Name

Dapagliflozin Tablets
(Brand Name: DIABIZ® 5 mg Tablets/DIABIZ® 10 mg Tablets)

2. Qualitative and Quantitative Composition

Each film-coated tablet contains:
Dapagliflozin propanediol USP equivalent to dapagliflozin …… 5 mg / 10 mg.
Colours: Erythrosine & Titanium Dioxide IP.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Dapagliflozin 5 mg and 10 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

Type 2 Diabetes

DIABIZ Tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Dapagliflozin is used as monotherapy when metformin is considered inappropriate due to intolerance. Dapagliflozin is also administered in combination with other antidiabetic agents.

Heart Failure

Dapagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Chronic Kidney Disease

Dapagliflozin is indicated in adults for the treatment of chronic kidney disease.

4.2 Posology and Method of Administration

For oral administration in adults. Assess renal function prior to initiation of dapagliflozin therapy and then as clinically indicated. Assess volume status and, if necessary, correct volume depletion prior to initiation of dapagliflozin therapy.

Type 2 Diabetes

The recommended starting dose is 5 mg of dapagliflozin once daily. If adequate glycemic control is not achieved, dose can be increased to 10 mg of dapagliflozin once daily.

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

Chronic Kidney Disease
The recommended dose is 10 mg of dapagliflozin once daily.

DIABIZ Tablets can be taken at any time of day with or without food.
Or, as prescribed by the physician.

4.3 Contraindications
DIABIZ Tablets are contraindicated in patients with known hypersensitivity to dapagliflozin or to any other excipient of the formulation.
DIABIZ Tablets are also contraindicated in patients on dialysis.

4.4 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 co-transporter 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.
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 (estimated glomerular filtration rate - 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

Reports of necrotizing fasciitis of the perineum (Fournier 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 such patients and treat appropriately.

4.5 Drug Interactions

Pharmacodynamic Interactions

Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues: Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, in patients with type 2 diabetes mellitus, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin.

Pharmacokinetic Interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolized by these CYP enzymes.

Effect of other medicinal products on dapagliflozin

Pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following co-administration of dapagliflozin with rifampicin (an inducer drug-metabolizing enzyme) a 22% decrease in dapagliflozin systemic exposure (area under the plasma concentration of a drug versus time curve - AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other CYP inducers (e.g., carbamazepine, phenytoin, phenobarbital, etc.) is not expected.

Following co-administration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

Dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin, or warfarin (or the anticoagulatory effects of warfarin). Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

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 of alternative methods to monitor glycemic control is advised.

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.

4.6 Use in Special Populations

Pregnant Women

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney. Therefore, DIABIZ Tablets are not recommended for use during pregnancy. When pregnancy is planned or detected, treatment with dapagliflozin should be discontinued immediately.

Lactating Women

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. However, animal studies have shown excretion of dapagliflozin and its metabolites in milk which produces pharmacologically-mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Thus, DIABIZ Tablets should not be used while breast-feeding.

Paediatric Patients

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

Geriatric Patients

Dose adjustments are usually not necessary for elderly patients. However, elderly patients may be at a greater risk for volume depletion and/or renal impairment, thus, dapagliflozin should be administered with caution in these patients.

Renal Impairment Patients

No dose adjustment is required based on renal function. It is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 ml/min/1.73 m^2. The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR < 45 ml/min/1.73 m^2 and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 ml/min/1.73 m^2, additional glucose lowering treatment should be considered in patients with diabetes mellitus.

Hepatic Impairment Patients

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

4.7 Effect on Ability to Drive and Use Machines

Dapagliflozin has no or negligible influence on the ability to drive and use machines. However, patients should be cautioned about the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylureas or insulin.

4.8 Undesirable Effects

The following adverse reactions have been reported as per the body system;

Infections: Vulvovaginitis, balanitis and genital mycotic infections, urinary tract infection, fungal infections and necrotising fasciitis of the perineum (Fournier's gangrene).

Metabolism and Nutrition Disorders: Hypoglycaemia (when used with sulphonylureas or insulin), volume depletion (dehydration, hypovolaemia, hypotension), thirst and diabetic ketoacidosis.

Nervous System Disorders: Dizziness.

Gastrointestinal Disorders: Constipation and dry mouth.

Skin and Subcutaneous Tissue Disorders: Rash and angioedema.

Musculoskeletal and Connective Tissue Disorders: Back pain.

Renal and Urinary Disorders: Dysuria, polyuria, nocturia, acute kidney injury, tubulointerstitial nephritis, urosepsis and pyelonephritis

Reproductive System and Breast Disorders: Vulvovaginal pruritus and genital pruritus.

Laboratory parameters: Increased haematocrit, increased serum creatinine, decreased eGFR, decreased creatinine renal clearance during initial treatment, dyslipidaemia, increased blood creatinine during initial treatment, increased blood urea, decreased body weight, increased low-density lipoprotein cholesterol (LDL-C) levels.

4.9 Overdose

There were no reports of overdosage with dapagliflozin. In clinical studies, dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50-times the maximum recommended human dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

5. Pharmacological Properties

5.1 Mechanism of Action

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). The SGLT2 is selectively expressed in the proximal renal tubules of kidney and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen.

Dapagliflozin does not inhibit other glucose transporters (present the in peripheral tissues) and is > 1,400 times more selective for SGLT2 than SGLT1 (the major transporter in the gut responsible for glucose absorption).

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic

effect) is observed after the first dose and it continuous over the 24-hour dosing interval. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and eGFR. Thus, in subjects with normal blood glucose and/or low eGFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia.
Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes.

5.2 Pharmacodynamic Properties

Following the oral administration of dapagliflozin in patients with type 2 diabetes mellitus, increase in the amount of glucose excreted in the urine was observed. Dapagliflozin doses of 5 mg 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. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus when dapagliflozin 10 mg per day was given for up to 2 years. After discontinuation of dapagliflozin 10 mg per day dose, on average, the elevation in urinary glucose excretion appears to be normal in 3 days.
This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA-β) has been observed in clinical studies with dapagliflozin.

5.3 Pharmacokinetic Properties

Absorption: Dapagliflozin is rapidly and well absorbed after oral administration. Following oral use, the maximum plasma concentration (C_{max}) reached 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%.

Effect of food/meal: 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. Thus, dapagliflozin can be administered with or without food.

Distribution: Plasma protein binding of dapagliflozin is approximately 91% and it does not alter in patients with renal or hepatic impairment. The mean steady-state volume of distribution of dapagliflozin is 118 liters.

Metabolism: Dapagliflozin is extensively metabolized, primarily to dapagliflozin 3-O-glucuronide, which is an inactive metabolite. The metabolism of dapagliflozin is primarily mediated by UGT1A9 (an enzyme present in the liver and kidney); CYP-mediated metabolism is a minor clearance pathway in humans.

Excretion: Dapagliflozin and its metabolites are primarily excreted via the renal pathway with less than 2% as unchanged dapagliflozin. Following a single 50 mg dose of [^{14}C]-dapagliflozin (radioactive), 75% and 21% of administered dose is excreted in urine and feces, respectively. In feces, approximately 15% of the dose is excreted as active (unchanged) drug. The mean terminal half-life (t½) of dapagliflozin is approximately 12.9 hours following a single oral dose of 10 mg in healthy subjects.

6. Nonclinical Properties

6.1 Animal Toxicology

Carcinogenesis: Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Mutagenesis: Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 μg/ml. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Impairment of Fertility: Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.

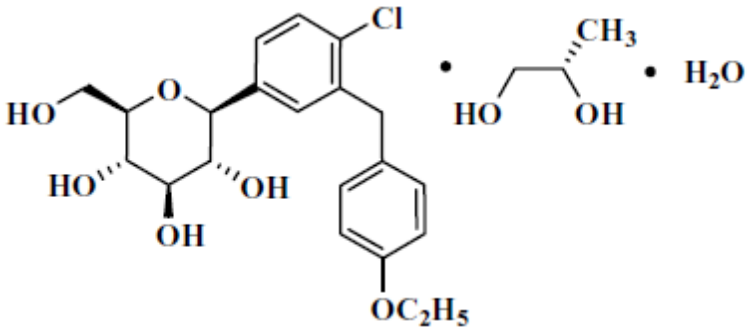
7. Description

Each tablet of DIABIZ 5 contains 5 mg of dapagliflozin as dapagliflozin propanediol monohydrate for oral administration in adults.
Each tablet of DIABIZ 10 contains 10 mg of dapagliflozin as dapagliflozin propanediol monohydrate for oral administration in adults.

DIABIZ 5mg/ 10 mg Tablets are pink colored, circular, biconvex, film coated tablets, plain on both sides.

Dapagliflozin propanediol is the propanediol form of dapagliflozin, a selective sodium-glucose co-transporter subtype 2 (SGLT2) inhibitor with antihyperglycemic activity. Dapagliflozin propanediol monohydrate is a hydrate that consists of dapagliflozin compounded with (S)-propylene glycol and hydrate in a (1:1:1) ratio.

Dapagliflozin propanediol occurs as a white to off-white non-hygroscopic powder.
Molecular Weight: 502.98 g/mol.
Molecular Formula: C21H25ClO6•C3H8O2•H2O.
Chemical Name: (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;(2S)-propane-1,2-diol;hydrate (1:1:1).
Structural Formula:



Inactive ingredients (excipients) of DIABIZ 5mg / DIABIZ 10 mg Tablet contain Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate. Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate, Triacetin, Talc, Starch, Titanium Dioxide and Erythrosine.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

24 months.

8.3 Packaging Information
15 tablets per strip.

8.4 Storage and Handling Instructions
Store protected from light and moisture at a temperature not exceeding 30 °C.
Keep out of the reach of children.

9. Patient Counseling Information
Instructions to Patients

- Patients should be advised to take this medicine as an adjuvant to diet and exercise to improve blood sugar levels. This drug therapy is not an alternative or substitute for diet and exercises; thus, patients should continue to follow a good lifestyle.
- Instruct patients to take this medicine exactly as prescribed by physician. Do not change the dose or stop therapy without consulting doctor.
- Patients are advised to take DIABIZ Tablets once a day, with or without food. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose at a time.
- If patients miss a dose, they can take it as soon as they remember. Do not take this medicine if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- Pregnant women should strictly avoid use of this medicine. When pregnancy is detected or planned, discontinue DIABIZ Tablets as soon as possible.
- Advise nursing women not to breastfeed during treatment with DIABIZ Tablets.
- Patients should be informed that while taking DIABIZ Tablets do not stop taking other prescription medicines, including other anti-diabetic medicines, without consulting their doctor.
- Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with dapagliflozin. Advise patients to immediately report any signs or symptoms suggesting these reactions and stop taking this medicine immediately.
- Patients should be informed that this medicine may cause dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). Risk of dehydration is higher if you take this medicine along with diuretics or if your age is above 65 years or if you are on a low salt diet or if you have kidney problems.

10. Details of Manufacturer
Synokem Pharmaceutical Ltd. Plot No. 56-57, Sector-6A, I.I.E (SIDCUL), Ranipur (BHEL), Haridwar – 249 403 (Uttarakhand).

11. Details of Permission or License Number with Date

Mfg Lic. No. : 27/UA/2018; Date of FDA Product Permission: 07/08/2021.

12. Date of Revision

January 2024.

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