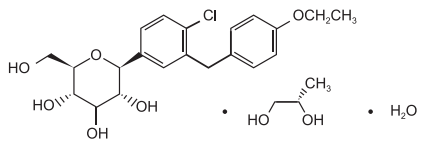
Daplyza™

[Dapagliflozin]

ڈیپلائزا

Film-coated Tablets 5mg & 10mg

DESCRIPTION
Daplyza (Dapagliflozin) is a highly potent, selective and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2).
Chemically, Dapagliflozin is 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 $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the structural formula is:



Dapagliflozin Propanediol Monohydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION
Daplyza (Dapagliflozin) is available for oral administration as:

Daplyza Tablets 5mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin…5mg

Daplyza Tablets 10mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin…10mg

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 and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

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 [^{14}C]-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 50mg 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 dapagliflozin 10mg.

Special Population
Patients with renal impairment
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 renal glucose clearance and 24hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. 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 10mg dapagliflozin. 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.

THERAPEUTIC INDICATIONS
Daplyza (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 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.

DOSAGE AND ADMINISTRATION
Prior to Initiation of Daplyza
Assess renal function prior to initiation of Daplyza (Dapagliflozin) therapy and then as clinically indicated. Assess volume status and, if necessary, correct volume depletion prior to initiation of Daplyza (Dapagliflozin).

Recommended Dosage
See Table below for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table: Recommended Dosage

eGFR (mL/min/1.73 m²)	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 (End Stage Kidney Disease), CV (Cardiovascular) death and hHF (hospitalization for heart failure).
On dialysis	Contraindicated.

*Daplyza (Dapagliflozin) is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45mL/min/1.73m².

Special Population
Patients with Hepatic Impairment
No dosage adjustment for Daplyza (Dapagliflozin) Tablets is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg when indicated.

Pediatric and Adolescent
The safety and efficacy of dapagliflozin in children aged 0 to <18 years have not been established.

Elderly
No dosage adjustment is recommended based on age.

CONTRAINDICATIONS
Dapagliflozin is contraindicated in patients with:
- History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema or to any excipient of the product.
- Patients who are being treated for glycemic control without established CVD or multiple CV risk factors with severe renal impairment, (eGFR less than 30mL/min/1.73m²).
- Patients on dialysis.

ADVERSE REACTIONS
Very Common: Hypoglycemia (when used with sulphonylurea or insulin).
Common: Vulvovaginitis, balanitis and related genital infections, urinary tract infection, diabetic ketoacidosis (when used in type 1 diabetes mellitus), dizziness, rash, back pain, dysuria, polyuria, hematocrit increased, creatinine renal clearance decreased during initial treatment and dyslipidemia.
Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal pruritus, pruritus genital, blood creatinine increased during initial treatment, blood urea increased and weight decreased.
Rare: Diabetic ketoacidosis (when used in Type 2 diabetes mellitus).
Very Rare: Necrotizing Fasciitis of the perineum (Fournier's gangrene) and angioedema.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

PRECAUTIONS
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/1.73m²), 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.

Ketoacidosis in Patients with Diabetes Mellitus
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. 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.
Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilized.

Type 2 Diabetes Mellitus: In patients where diabetic ketoacidosis is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.
Restarting SGLT2 inhibitor treatment in patients experiencing a diabetic ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

Type 1 Diabetes Mellitus: Dapagliflozin should not be initiated when patients are at a higher risk of diabetic ketoacidosis, such as:
- Patients with low insulin needs.
- Patient not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and who are unlikely to maintain adequate insulin dosing.
- Patients with increased insulin requirements due to acute medical illness or surgery.
- Patients who insist on maintaining caloric restriction, carbohydrate restriction or ketogenic diet or who chronically under-dose insulin (e.g. in order to remain in a lipolytic state).
- Patients with recent or recurrent history of diabetic ketoacidosis.
- Patients with elevated ketones levels (BHB reading is greater than 0.6mmol/L or urine ketones one plus (+)). If ketones are elevated (blood beta-hydroxybutyrate reading 0.6mmol/L or greater), treatment with dapagliflozin should not be started until the ketone levels are normal.
- Patients unable or unwilling to monitor ketones.
- Patients with excessive alcohol consumption or who use illicit drugs.

Patients using an insulin infusion pump have a higher risk of diabetic ketoacidosis. Insulin injections should be given within 2 hours of an unexplained high blood glucose/ketone value and dapagliflozin treatment should be interrupted.
Restarting SGLT2 inhibitor treatment in patients experiencing a diabetic ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

During treatment with dapagliflozin:
- Insulin therapy should be continuously optimized.
- When needed to prevent hypoglycemia, insulin dose reduction should be done cautiously to avoid ketosis and diabetic ketoacidosis.
- In the event of a marked reduction of insulin need, discontinuation of dapagliflozin should be considered.

Ketone monitoring: The patient should be advised to test their ketone level (urine or blood) if signs or symptoms of ketoacidosis occur. Measurement of blood ketone levels is preferred to urine. Ketones should be monitored on a regular basis during the initial one to two weeks, then the frequency of ketone level testing should be individualized, according to the patient's lifestyle and/or risk factors. Ketone levels should be also checked in situations that may predispose to or increase risk of diabetic ketoacidosis.

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)
A rare but serious and life-threatening necrotizing infection, Necrotizing fasciitis of the perineum (Fournier's Gangrene) have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. 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.

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.

Surgery
Treatment with dapagliflozin should be ceased prior to major surgery. Consider temporarily discontinuing dapagliflozin for at least 3 days prior to surgery.

Elderly (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.
Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Lower Limb Amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine Laboratory Assessments
Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine.

Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 hypoglycemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

Limitation of Use
- 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 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.

Pregnancy
Dapagliflozin must not be used during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Nursing Mothers
Dapagliflozin must not be used by breastfeeding women. It is not known whether dapagliflozin or its metabolites are excreted in human milk.

DRUG 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 hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of 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.

OVERDOSAGE
Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500mg (50 times the maximum recommended human dose). In clinical studies where once-daily doses of up to 100mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycemia was slightly higher than placebo and was not dose-related.

Treatment
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 hemodialysis has not been studied.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Daplyza (Dapagliflozin) Tablets 5mg are available in pack of 14's.
Daplyza (Dapagliflozin) Tablets 10mg are available in pack of 14's.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
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