Daploz®

(Dapagliflozin)

Highnoon

COMPOSITION
Daploz 5mg Tablet: Each film-coated tablet contains:
Dapagliflozin (as Propanediol Monohydrate) 5mg
Daploz 10mg Tablet: Each film-coated tablet contains:
Dapagliflozin (as Propanediol Monohydrate) 10mg

DESCRIPTION
Dapagliflozin is a sodium-glucose co-transport 2 inhibitor that enhances urinary excretion of glucose by renal glucose reabsorption.

MECHANISM OF ACTION
Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycemia in type 2 diabetes, reabsorption of filtered glucose continues. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action. Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

PHARMACOKINETICS
Peak plasma concentrations of dapagliflozin occur within 2 to 3 hours after an oral dose, with a bioavailability of about 78%. It is about 91% bound to plasma proteins. Dapagliflozin is extensively metabolized to inactive metabolites via uridine diphosphate glucuronosyltransferase UGT1A9 in the liver and kidney. It has a plasma terminal half-life of about 13 hours; about 75% of the dose is excreted in the urine and 21% in the faeces.

INDICATIONS AND USAGE
It is indicated in the following;

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

DOSAGE AND ADMINISTRATION
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. It 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 . Dapagliflozin is likely to be ineffective in this setting based upon its mechanism of action.

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: It is contraindicated.

- 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.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema.
- Patients on dialysis
- Ketoacidosis

WARNINGS AND PRECAUTIONS

- Dapagliflozin causes intravascular volume contraction. Dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy. It is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness. Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. Careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including hematocrit) and electrolytes is recommended for patients receiving it.
- 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. Before initiating dapagliflozin, consider factors in the patient history (such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness) 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). Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted once the patient's condition has stabilized.
- Dapagliflozin causes intravascular volume depletion and can cause renal impairment. There have been reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin; some reports involved patients younger than 65 years of age .Before initiating dapagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics ,ACE inhibitors,ARBs,NSAIDs).Consider temporarily discontinuing dapagliflozin in any setting of reduced oral intake (such as acute illness or fasting)or fluid losses (gastrointestinal illness or excessive heat exposure),monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue dagagliflozin promptly and initiate treatment. Dapagliflozin increases serum creatinine and decreases e GFR.
  Elderly patients and patients with impaired renal function may be more susceptible to these changes. Renal function should be evaluated prior to initiation of dapagliflozin is not recommended in patients with an e GFR less than 30ml/min/1.73m².
- There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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.
- 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.
- 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.
- Increases in LDL-C occurs with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating dapagliflozin.
- Dapagliflozin should not be used in patients with active bladder cancer (a causal relationship between dapagloflozin and bladder cancer is unlikely). There is insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with dapagliflozin should be considered.
- Hematocrit increase was observed with dapagliflozin treatment, therefore, caution in patients with already elevated hematocrit is warranted.
- An increase in case of lower limb amputation (primarily of the toe) has been observed, with another SGLT2 inhibitor. Like for all diabetic patients it is important to counsel patients on routine preventive foot care.
- Patients taking this medicinal product will test positive for glucose in their urine.
- Dapagliflozin have no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycemia.
- 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 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.

ADVERSE REACTIONS
The reported adverse events are; hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, genital mycotic infections, increases in low-density lipoprotein cholesterol (LDL-C), bladder cancer, female genital mycotic infections (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 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 infection (balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, posthitis), nausea, influenza, dyslipidemia, constipation, discomfort with urination, pain in extremity, osmotic diuresis (reductions in intravascular volume), volume depletion (including dehydration, hypovolemia, orthostatic hypotension, or hypotension), impairment of renal functions (increases in serum creatinine, decreases in eGFR, renal failure), bone fractures, hypoglycemia, hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity), rash, increase hematocrit, hyperphosphatemia, increase in low density lipoprotein cholesterol, breast cancer, prostate cancer, hyperhidrosis, dizziness, dry mouth, thirst, weight decreased, and decrease in serum bicarbonate.

DRUG INTERACTIONS

- 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.
- 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.
- Dapagliflozin product may add the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

USE IN SPECIFIC POPULATIONS

Pregnancy
Dapagliflozin is not recommended during the second and third trimesters of pregnancy. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Lactation
There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of dapagliflozin is not recommended while breastfeeding.

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

Geriatric Use
No dosage change is recommended based on age. In patients ≥ 65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure.

Renal Impairment
It was associated with increases in serum creatinine and decreases in eGFR. Patients with diabetes and renal impairment using dapagliflozin may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion.
Use of dapagliflozin for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73m² . Efficacy and safety of dapagliflozin in patients with an eGFR less than 25 mL/min/1.73m² were not evaluated. It 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.

OVERDOSAGE
In the event of an overdose, employ reasonable supportive measures, as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Daploz 5mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Daploz 10mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.

ڈیپلوز®

(ڈیپاگلیفلوزن)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14003003