# Daglozin™
(Dapagliflozin)

10mg 5mg Tablets

# ڈیگلوزِن
۵ ملی گرام
۱۰ ملی گرام
(ڈاپاگلافلوزن) ٹیبلٹس

## QUALITATIVE AND QUANTITATIVE COMPOSITION

**Daglozin™ Tablets 5mg**
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate eq.
to Dapagliflozin.....5mg
Innovator's Specs.

**Daglozin™ Tablets 10mg**
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate eq.
to Dapagliflozin.....10mg
Innovator's Specs.

## 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.

## 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. **Pharmacokinetics: Absorption:** Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax 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 Cmax by up to 50% and prolongs tmax 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 [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 ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of Daglozin 10 mg. **Pharmcodynamics:** 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.

## INDICATIONS AND USAGE

Daglozin (dapagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, as monotherapy (if metformin inappropriate). Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control). **Limitations of Use:** Daglozin is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. **Contraindications:** Ketoacidosis, History of a serious hypersensitivity reaction to Daglozin. Severe renal impairment, (eGFR less than 30 mL/min/1.73 $m^2$) end-stage renal disease (ESRD), or patients on dialysis.

## INTERACTIONS

### DRUG INTERACTIONS

**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 SPECIFIC POPULATION

**Pregnancy:** Avoid- toxicity in animal studies. **Breast Feeding:** Avoid present in milk in animal studies. **Hepatic Impairment:** Initial dose 5 mg daily in severe impairment, increased according to response. **Renal Impairment:** Avoid if eGFR less than 60 mL/minute/1.73 $m^2$ (ineffective). **Monitoring Requirements:** Determine renal function before treatment and at least annually thereafter.

## PRECAUTIONS

**Hypotension:** causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Daglozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics. **Electrolyte Disturbances:** For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. **Raised haematocrit:** Haematocrit increase was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted. **Lower limb amputations:** 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. **Lactose:** The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product. **Ketoacidosis:** Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2)

inhibitors. **Acute Kidney Injury and Impairment in Renal Function:** Daglozin causes intravascular volume contraction, and can cause renal impairment. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving Daglozin; some reports involved patients younger than 65 years of age. Use of Daglozin is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 $m^2$ and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 $m^2$. **Urosepsis and Pyelonephritis:** There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. Daglozin 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 Daglozin. **Genital Mycotic Infections:** Daglozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. **Increases in Low-Density Lipoprotein Cholesterol (LDL-C):** Daglozin Increases in LDL-C. Monitor LDL-C and treat per standard of care after initiating Daglozin. **Bladder Cancer:** There are insufficient data to determine whether Daglozin has an effect on pre-existing bladder tumors. Consequently, Daglozin should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with Daglozin should be considered.

## IMPORTANT SAFETY INFORMATION

**MHRA: Risk of diabetic ketoacidosis with Sodium Glucose Co-Transporter 2 (SGLT2) (Dapagliflozin):** A review by the European Medicines Agency has concluded that serious, life threatening, and fatal cases of diabetic ketoacidosis (DKA) have been reported rarely in patients taking an SGLT2 inhibitor. In several cases, the presentation of DKA was atypical with patients having only moderately elevated blood glucose levels, and some of them occurred during off label use. To minimize the risk of such effects when treating patients with a SGLT2 inhibitor, the European **Medicines Agency has issued the following advice:** Inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat), and advise them to seek immediate medical advice if they develop any of these. test for raised ketones in patients with signs and symptoms of DKA, even if plasma levels are near normal. use Dapagliflozin with caution in patients with risk factors for DKA, (including a low beta cell reserve, conditions leading to restricted food intake or severe dehydration, sudden reduction in insulin, increased insulin requirements due to acute illness, surgery or alcohol abuse), and discuss these risk factors with patients. discontinue treatment if DKA is suspected or diagnosed. do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved. interrupt SGLT2 treatment in patients who are hospitalized for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilized.

## DOSAGE AND ADMINISTRATION

**Adult 18-74 Years:** The recommended starting dose is 5mg once daily, taken in the morning, with or without food. Dose can be increased to 10 mg once daily in patients tolerating Daglozin who require additional glycemic control. Assess renal function before initiating Daglozin and periodically thereafter. **Adult 75 years and over:** initiation not recommended. Initiation is

not recommended in patients with an eGFR less than 60 mL/min/1.73 $m^2$. Use of Daglozin is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 $m^2$. **Overdosage:** 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.

## ADVERSE REACTIONS

**The following important adverse reactions are described below:** Hypotension, Ketoacidosis, Acute Kidney Injury and Impairment in Renal Function, Urosepsis and Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues, Genital Mycotic Infections, Increases in Low-Density Lipoprotein Cholesterol (LDL-C), Bladder Cancer. **Common or very common:** Back pain, constipation, dyslipidaemia, dysuria, genital infection, hypoglycaemia (in combination with insulin or sulphonylurea), polyuria, sweating, thirst, urinary-tract infection. **Uncommon:** Dehydration, dizziness, hypotension, hypovolaemia, nausea, nocturia, raised serum creatinine, raised serum urea, rash.

## DOSAGE

As directed by the physician.

## INSTRUCTIONS

Store at 20°C-25°C, excursions permitted to 15°C-30°C. Protect from light and moisture. Keep all medicines out of the reach of children.

## PRESENTATION

Daglozin™ (Dapagliflozin) Tablets 5mg are available in Alu-Alu blister pack of 1x10's with leaflet.
Daglozin™ (Dapagliflozin) Tablets 10mg are available in Alu-Alu blister pack of 1x10's with leaflet.

## علامات/طریقہ استعمال

**ڈیگلوزِن** ٹائپ ۲ ذیابیطس کے ان مریضوں میں علاج کے لئے تجویز کردہ ہے۔

## مضر اثرات

بلڈ پریشر کا کم ہونا، کیٹو ایسیڈوسز، گردوں کی خرابی، یوروسیپسس، کولیسٹرول کا بڑھنا، جینیٹل فنگل انفیکشنز، مثانے کا کینسر۔

## احتیاطی تدابیر

بچے، حاملہ خواتین اور دودھ پلانے والی مائیں صرف ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۷۵ سال اور اس سے زائد عمر کے مریضوں میں بلڈ پریشر کم ہونے کا خدشہ ہوسکتا ہے۔
۸۵ سال اور اُس سے زائد عمر کے مریضوں میں **ڈیگلوزِن** کا استعمال ممنوع ہے۔
جگر اور گردے کے مریضوں میں **ڈیگلوزِن** کا استعمال ممنوع ہے۔

**خوراک:** ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
**ہدایات:** ۲۰ سے ۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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