Daglozin™-M

(Dapagliflozin+Metformin HCl)

5mg+850mg, 5mg+1000mg Tablets

ڈیگلوزِن-ایم

ٹیبلٹس

۵ ملی گرام + ۸۵۰ ملی گرام

۵ ملی گرام + ۱۰۰۰ ملی گرام

(ڈاپاگلائفلوزِن/میٹ فورمن ایچ سی ایل)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Daglozin™-M Tablets 5mg+850mg

Each film-coated tablet contains:

Dapagliflozin Propanediol Monohydrate eq. to Dapagliflozin….....5mg

Metformin HCl U.S.P. 850mg

Innovator's Specification

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DESCRIPTION

Daglozin-M (dapagliflozin and metformin HCl) tablets contain two oral antihyperglycemic medications used in the management of type 2 diabetes: dapagliflozin and metformin hydrochloride.

CLINICAL PHARMACOLOGY

Mechanism of Action: Daglozin-M combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin: Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2. The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

Metformin: Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- By modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization in muscle;
- By delaying intestinal glucose absorption

Pharmacokinetic properties: Daglozin-M combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride administered together as individual tablets.

Dapagliflozin: Absorption: Dapagliflozin was rapidly and well absorbed after oral administration. The absolute oral bioavailability of dapagliflozin following the administration of a 10-mg dose is 78%. **Distribution:** Dapagliflozin is approximately 91% protein bound. The mean steady-state volume of distribution of dapagliflozin was 118 liters.

Biotransformation: Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects.
Elimination: The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.
Metformin HCl: Absorption: After an oral dose of metformin, tmax is reached in 2.5 h. Plasma protein binding is negligible. Metformin partitions into erythrocytes.
Distribution: Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean Vd ranged between 63-276 L.
Biotransformation: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination: Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

INDICATIONS AND USAGE

Daglozin-M is indicated in adults aged 18 years-74 years with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:
• In patients inadequately controlled on their maximally tolerated dose of metformin alone
• In combination with other glucose-lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products.
• In patients, already being treated with the combination of dapagliflozin and metformin as separate tablets.

CONTRAINDICATIONS

Dapagliflozin/Metformin HCl is contraindicated in patients with:
• Hypersensitivity to the active substances or to any of the excipients.
• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis); diabetic pre-coma; severe renal failure (GFR < 30 mL/min)
• Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
• Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock.
• Hepatic impairment, acute alcohol intoxication, alcoholism.

INTERACTIONS

Coadministration of multiple doses of dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects. No interaction studies have been performed for Dapagliflozin/Metformin HCl. The following statements reflect the information available on the individual active substances.
Dapagliflozin: Pharmacodynamic interactions: Diuretics: This medicinal product 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, 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, this medicinal product is not expected to alter the metabolic clearance of coadministered

medicinal products that are metabolised by these enzymes. Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Metformin: Concomitant use not recommended: Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems.

Alcohol: Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance of this medicinal product. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents: Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis.

Combination requiring precautions for use: Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic activity. Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting, or using such products in combination with metformin, close monitoring of renal function is necessary.

USE IN SPECIFIC POPULATION

Pregnancy: It is not recommended during the second and third trimesters of pregnancy.

Lactation: It should not be used while breast-feeding.

Pediatric Use: Safety and effectiveness of Dapagliflozin/Metformin HCl in pediatric patients under 18 years of age have not been established.

Geriatric Use: No dosage change is recommended based on age.

Renal impairment: It is not recommended for use in patients with moderate to severe renal impairment (patients with GFR < 60 mL/min).

Hepatic impairment: Avoid.

PRECAUTIONS

Lactic acidosis: Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. Patients and/or care-givers should be informed on the risk of lactic acidosis.

Renal function: Renal function should be assessed, before initiation of treatment and regularly thereafter. If renal function falls below GFR <60 mL/min, treatment should be discontinued. Metformin is contraindicated in patients with GFR of <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances: Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. This medicinal product is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).

Diabetic ketoacidosis: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. It is not known if DKA is more likely to occur with higher doses of dapagliflozin. The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately. Treatment should be inter-

rupted 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.

Urinary tract infections: Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of treatment should be considered when treating pyelonephritis or urosepsis.

Use in patients treated with pioglitazone: While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, this medicinal product is not recommended for use in patients concomitantly treated with pioglitazone.

Elevated 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.

Surgery: Dapagliflozin/Metformin HCl must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

ADVERSE REACTIONS

Very common: Hypoglycaemia (when used with Sulfonylureas or insulin), gastrointestinal symptoms.

Common: Vulvovaginitis, balanitis and related genital infections, Urinary tract infection, Taste disturbance, dizziness, rash, dysuria, polyuria, pain, Haematocrit increased, creatinine renal clearance decreased, dyslipidaemia **Uncommon:** Fungal infection, volume depletion, thirst, Constipation, dry mouth, nocturia, renal impairment, vulvovaginal pruritus, pruritus genital. **Rare:** Diabetic ketoacidosis, Lactic acidosis, Vitamin B12 deficiency, liver function disorders, hepatitis, Urticaria, Erythema Pruritus, blood creatinine increased, blood urea increased, weight decreased.

DOSAGE AND ADMINISTRATION

Adults with normal renal function (GFR ≥ 90 mL/min): For patients inadequately controlled on metformin monotherapy or metformin in combination with other glucose-lowering medicinal products including insulin. The recommended dose is one tablet twice daily.

For patients switching from separate tablets of dapagliflozin and metformin: Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to Daglozin-M should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Patients with renal impairment: No dose adjustment is recommended for patients with mild renal impairment. GFR 60–89 mL/min. The maximum daily dose is 3000 mg metformin and should preferably be divided into 2–3 daily doses. Daglozin-M is not recommended for use in patients with GFR <60mL/min.

Method of administration: Daglozin-M should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

For Adults 75 Years and over: Initiation not recommended.

Overdose: Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis.

INSTRUCTIONS

Dosage as directed by the physician. Store below 30°C. Protect from heat, light and moisture.
Keep all medicines out of the reach of children.

PRESENTATION

Daglozin-M (Dapagliflozin/Metformin HCl) Tablets 5mg/850mg are available in Alu-Alu blister pack of 28 tablets.
Daglozin-M (Dapagliflozin/Metformin HCl) Tablets 5mg/1000mg are available in Alu-Alu blister pack of 28 tablets.

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(ڈاپاگلائفلوزِن/میٹ فورمن ایچ سی ایل)

علامات/طریقہ استعمال

ڈیگلوزن-ایم ٹائپ ۲ ذیابیطس کے 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 ڈیگلوزن-ایم کا استعمال ممنوع ہے۔
جگر اور گردے کے مریضوں میں ڈیگلوزن-ایم کا استعمال ممنوع ہے۔

ہدایات

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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ISO 9001:2015 ISO 14001:2015 ISO 45001:2018

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