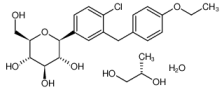
DAPANEXT-M Tablet

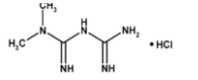
(As per Innovator's Specifications)
Dapagliflozin
(USP Specification)
Metformin HCL
(USP Specification)
5/850mg & 5/1000mg film-coated tablets

DESCRIPTION

Dapanext-M (Dapagliflozin + Metformin HCL) contains two oral anti-hyperglycemic medications used in the management of type 2 diabetes: Dapagliflozin and Metformin HCL. Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. Chemically, Dapagliflozin is 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). Its molecular formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the structural formula is:



Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. It has a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and the structural formula is:



COMPOSITION

Dapanext-M Tablets 5/850mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin...5mg & Metformin HCl ...850mg
(As per Innovator's Specifications)
Dapanext-M Tablets 5/1000mg
Each film-coated tablet contains:
Dapagliflozin Propanediol Monohydrate equivalent to Dapagliflozin...5mg & Metformin HCl ...1000mg
(As per Innovator's Specifications)

CLINICAL PHARMACOLOGY

Mechanism of Action

Dapagliflozin

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.

Metformin Hcl

It is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin HCl stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin HCl may active via three mechanisms;

• By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

• In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization.

• By delaying intestinal glucose absorption.

Pharmacokinetics

Absorption

Dapagliflozin

After oral administration, Dapagliflozin is rapidly absorbed with maximum plasma concentrations (Cmax) usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state Dapagliflozin Cmax and AUCT values following once daily 10mg doses of Dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of Dapagliflozin following the administration of a 10mg dose is 78%.

Metformin HCl

After an oral dose of Metformin HCl, tmax is reached in 2.5 h. Absolute bioavailability of a 500mg or 850mg Metformin HCl tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in feces was 20-30%. After oral administration, Metformin HCl absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Metformin HCl absorption is non-linear. At the usual Metformin HCl doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1µg/mL.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of Dapagliflozin was 118 litres.

Metformin HCl

Metformin HCl is negligibly bound to plasma proteins. Metformin HCl partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63-276 l.

Metabolism

Dapagliflozin

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. The formation of Dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Metformin HCl

Metformin HCl is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Dapagliflozin

The mean plasma terminal half-life (t1/2) for Dapagliflozin was 12.9 hours following a single oral dose of Dapagliflozin 10mg to healthy subjects. The mean total systemic clearance of Dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged Dapagliflozin. After administration of a 50mg [14C]-Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Metformin Hcl

Renal clearance of Metformin HCl is >400mL/min, indicating that Metformin HCl is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

Special population

Patients with renal impairment

Dapagliflozin

At steady-state (20mg once-daily Dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of Dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on Dapagliflozin exposure is not known.

Metformin HCL

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of Metformin HCl is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance, leading to increased levels of Metformin HCl in plasma.

Patients with hepatic impairment

Dapagliflozin

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of Dapagliflozin were up to 12% and 36% higher, respectively, compared with healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of Dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Metformin HCL

No pharmacokinetic studies of Metformin HCl have been conducted in subjects with hepatic impairment.

THERAPEUTIC INDICATIONS

Dapanext-M (Dapagliflozin + Metformin HCl) is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise:

• In patients insufficiently controlled on their maximally tolerated dose of Metformin HCl alone.

• In combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with Metformin HCl and these medicinal products.

• In patients already being treated with the combination of Dapagliflozin and Metformin HCl as separate tablets. Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

DOSAGE AND ADMINISTRATION

Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)

The recommended dose of Dapanext-M (Dapagliflozin + Metformin HCl) is one tablet twice daily.

For patients insufficiently controlled on Metformin HCl monotherapy or Metformin HCl in combination with other medicinal products for the treatment of diabetes

Patients insufficiently controlled on Metformin HCl alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of Dapanext-M (Dapagliflozin + Metformin HCl) equivalent to Dapagliflozin 10mg, plus the total daily dose of Metformin HCl, or the nearest therapeutically appropriate dose, already being taken. When Dapanext-M (Dapagliflozin + Metformin HCl) is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycemia.

Patients switching from separate tablets of Dapagliflozin and Metformin Hcl

Patients switching from separate tablets of Dapagliflozin (10mg total daily dose) and Metformin HCl to Dapanext-M(Dapagliflozin + Metformin HCl), should receive the same daily dose of Dapagliflozin and Metformin HCl already being taken or the nearest therapeutically appropriate dose of Metformin HCL.

Special Population

Patients with renal impairment

Renal function should be assessed before initiation of treatment with Metformin HCl containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. No dose adjustment of Dapanext-M(Dapagliflozin + Metformin HCl) is needed in patients with an eGFR greater than or equal to 45mL/min/1.73 m2

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Dapanext-M (Dapagliflozin + Metformin HCl) is not recommended in patients with an eGFR below 45mL/min/ 1.73 m2

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Patients with hepatic impairment

Dapanext-M (Dapagliflozin + Metformin HCl) must not be used in patients with hepatic impairment.

Elderly

Dapanext-M (Dapagliflozin + Metformin HCl) should be used with caution in elderly patients.

Monitoring of renal function is necessary to aid in prevention of Metformin HCl-associated lactic acidosis, particularly in elderly patients.

Pediatric population

The safety and efficacy of Dapanext-M (Dapagliflozin + Metformin HCl) in children and adolescents aged 0 to <18 years have not yet been established.

Method of administration

Dapanext-M (Dapagliflozin + Metformin HCl) should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with Metformin Hcl.

CONTRAINDICATIONS

The combination of Dapagliflozin and Metformin HCl is contraindicated in:

• Patients with hypersensitivity to Dapagliflozin, Metformin HCl or to any of the excipient of the product.

• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

• Severe renal failure (eGFR below 30mL/ min/ 1.73m2), end stage renal disease or patients on dialysis.

• Diabetic pre-coma.

• 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.

ADVERSE REACTIONS

Very Common: Hypoglycemia (when used with sulphonylurea or insulin) and gastrointestinal symptoms.

Common: Vulvovaginitis, balanitis and related genital infections, urinary tract infection, taste disturbance, dizziness, rash, back pain, dysuria, polyuria, haematocrit increased, creatinine renal clearance decreased during initial treatment and dyslipidaemia.

Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal pruritus, pruritis genital, blood creatinine increased during initial treatment, blood urea increased and weight decreased.

Rare: Diabetic ketoacidosis.

Very Rare: Fournier's gangrene, lactic acidosis, vitamin B12 deficiency, liver function disorders, hepatitis, urticaria, erythema and pruritus.

Lactic Acidosis

Lactic acidosis is a serious metabolic complication, mostly occurs due to acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin HCl accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhea or vomiting, fever or reduced fluid intake), Metformin HCl should be temporarily discontinued. Medicines that can acutely impair renal function (such as antihypertensive,diuretics and NSAIDs) should be initiated with caution in Metformin HCl-treated patients.

General

Dapagliflozin + Metformin HCl should not be used in patients with type 1 diabetes.

Use in patients at risk for volume depletion and/or hypotension

Caution should be exercised in patients for whom a Dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

Diabetic ketoacidosis

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 diabetic ketoacidosis is suspected or diagnosed, treatment with Dapagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended inthese 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. Before initiating Dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. If Fournier's gangrene is suspected, Dapagliflozin + Metformin HCl should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

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.

Elderly

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

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 diabetes patients it is important to counsel patients on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking this medicinal product will test positive for glucose in their urine.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in Metformin HCl accumulation and an increased risk of lactic acidosis. Metformin HCl should be discontinued prior to start time of the imaging procedure and not restarted until 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Surgery

Dapagliflozin + Metformin HCl must be discontinued at the time of surgery with general, spinal or epidural anesthesia. 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.

Effects on ability to drive and use machines

Dapagliflozin + Metformin HCl has 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.

Pregnancy

The use of this medicinal product is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with Dapagliflozin + Metformin HCl should be discontinued.

Nursing Mothers

Metformin HCl is excreted into human breast milk. It is unknown whether Dapagliflozin is excreted in human milk. Dapagliflozin + Metformin HCl should not be administered during nursing.

DRUG INTERACTIONS

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.

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 or 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 when used in combination with Dapagliflozin + Metformin HCl.

Drugs that Reduce Metformin HCl Clearance

Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with Metformin HCl by competing for common renal tubular transport systems. Therefore, close monitoring of glycemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are coadministered.

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis. Therefore, consumption of alcohol should be avoided.

NSAIDs, ACE Inhibitors, angiotensin II receptor antagonists and diuretics

These medicinal products can adversely affect renal function which may increase the risk of lactic acidosis when given in combination with Metformin HCl. Therefore, close monitoring of renal function is necessary.

Glucocorticoids beta-2-agonists and diuretics

Glucocorticoids, beta-2 agonists and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

OVERDOSAGE

Dapagliflozin

Single doses of up to 500mg Dapagliflozin (equivalent to 50-times the maximum recommended human dose) did not show any toxicity. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin HCl

High overdose or concomitant risks of Metformin-HCl may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

STORAGE

Do not store above 30°C.

Protect from sunlight and moisture.

HOW SUPPLIED

Dapanext-M (Dapagliflozin + Metformin HCl) Tablets 5mg + 850mg are available in pack of 14's and 28's

Dapanext-M (Dapagliflozin + Metformin HCl) Tablets 5mg + 1000mg are available in pack of 14's and 28's

Keep out of the reach of children.

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

Lactose & Gluten Free

ڈیپانیکسٹ-ایم ٹیبلٹ

(ڈیپاگلافلوزن + میٹفارمین ایچ سی ایل)

5ملی گرام +850ملی گرام

5ملی گرام +1000ملی گرام

فلم کوٹڈ گولیاں

خوراک و ہدایات:

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر

روشنی اور نمی سے محفوظ رکھیں۔

NEXT PHARMACEUTICAL

Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
Plot no. 44-A&B, Sunder Industrial Estate Lahore-Pakistan