Dapxiga-M

(Dapagliflozin and Metformin HCl Tablets)

4000003179

Product Specifications: Innovator
Dapxiga-M Tablets 5mg/850mg
Each film coated tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin 5mg
Metformin Hydrochloride U.S.P. 850mg
Dapxiga-M Tablets 5mg/1000mg
Each film coated tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin 5mg
Metformin Hydrochloride U.S.P. 1000mg

DESCRIPTION

Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) 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. 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 C21H25ClO6•C3H8O2•H2O and the formula weight is 502.98.

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 hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of C4H11N5•HCl and a molecular weight of 165.63.

CLINICAL PARTICULARS

Therapeutic indications

Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) 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 alone
• in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these medicinal products
• in patients already being treated with the combination of dapagliflozin and metformin as separate tablets.

Posology and method of administration

Posology

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

The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin.

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

Patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) 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 hypoglycaemia.

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 Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Special populations

Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing medicinal products and at least annually thereafter. In patients at 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.

If no adequate strength of Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) is available, individual mono-components should be used instead of the fixed dose combination.

Dosage in patients with renal impairment

GFR mL/min	Metformin	Dapagliflozin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 10 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 10 mg. The glucose lowering efficacy of dapagliflozin is reduced.
< 30	Metformin is contraindicated.	Maximum daily dose is 10 mg. Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. The glucose lowering efficacy of dapagliflozin is likely absent.

Hepatic impairment: This medicinal product must not be used in patients with hepatic impairment.

Elderly (≥ 65 years): Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients.

Pediatric population: The safety and efficacy of Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Method of administration: Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

Contraindication

- 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

SERIOUS WARNINGS AND PRECAUTION BOX

Lactic Acidosis

• Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Dapxiga-M (Dapagliflozin and Metformin HCl Tablets).
• Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Dapxiga-M (Dapagliflozin and Metformin HCl Tablets), since alcohol intake potentiates the effect of metformin on lactate metabolism.

Diabetic Ketoacidosis

• Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with dapagliflozin and other sodium-glucose cotransporter 2 (SGLT2) inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL). Some cases of DKA have been fatal.
• Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level. If DKA is suspected or diagnosed, Dapxiga-M should be **discontinued immediately.**
• Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) is contraindicated for the treatment of DKA or in patients with a history of DKA.
• Dapxiga-M (Dapagliflozin and Metformin HCl Tablets) is contraindicated in patients with type 1 diabetes.

WARNINGS AND PRECAUTIONS

Lactic acidosis: Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Dapagliflozin + Metformin HCl combination should be temporarily discontinued and contact with a health care professional is recommended. Patients and/or care-givers should be informed on the risk of lactic acidosis. In case of suspected symptoms, the patient should stop taking Dapagliflozin + Metformin HCl combination and seek immediate medical attention.

Renal function: The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with GFR < 45 mL/min and is likely absent in patients with severe renal impairment. Metformin is excreted by the kidney, and moderate to severe renal insufficiency increases the risk of lactic acidosis. Renal function should be assessed before initiation of treatment and regularly thereafter. Metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function. Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a NSAID.

Use in patients at risk for volume depletion and/or hypotension: Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with high blood glucose concentrations. 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. In case of intercurrent conditions that may lead to volume depletion careful monitoring of volume status is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised 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 stabilised. Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. SGLT2 inhibitors should be used with caution in patients who may be at higher risk of DKA. Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of Dapagliflozin + Metformin HCl combination in patients with type 1 diabetes have not been established and Dapagliflozin + Metformin HCl combination should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies, DKA was reported with common frequency.

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 combination 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 (≥ 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.

Cardiac failure: Experience with dapagliflozin in NYHA class IV is limited.

Lower limb amputations: An increase in cases of lower limb amputation (primarily of the toe) has been observed in 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.

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

Surgery: Dapagliflozin + Metformin HCl combination 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.

Change in clinical status of patients with previously controlled type 2 diabetes: As this medicinal product contains metformin, a patient with type 2 diabetes previously well-controlled on it who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for

evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no data from the use of Dapagliflozin + Metformin HCl combination or dapagliflozin in pregnant women. Studies in rats treated with dapagliflozin have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of this medicinal product is not recommended during the second and third trimesters of pregnancy. A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development. When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product.

Breast-feeding

It is unknown whether this medicinal product or dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used while breast-feeding.

Fertility: The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. For metformin, studies in animals have not shown reproductive toxicity.

DRUG INTERACTIONS

Coadministration of multiple doses of dapagliflozin and metformin does not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects. 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

Effect of other medicinal products on dapagliflozin: Following coadministration of dapagliflozin with rifampicin, no dose adjustment is recommended. Following coadministration of dapagliflozin with mefenamic acid, no dose adjustment is recommended.

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.

Paediatric population: Interaction studies have only been performed in adults.

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. Therefore, close monitoring of glycaemic 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 co administered.

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.

Combination requiring precautions for use: Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycaemic 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 glucose-lowering medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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.

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 metformin.

Adverse Reactions

The following adverse reactions have been identified in the placebo-controlled dapagliflozin plus metformin clinical studies, dapagliflozin clinical studies and metformin clinical studies and post-marketing experience. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Very common: Hypoglycaemia(when used with SU or insulin), 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, Dyslipidaemia.

Uncommon: Fungal Infection, Volume Depletion, Thirst, Constipation, Dry mouth, Nocturia, Vulvovaginal pruritus, Pruritus genital, Blood creatinine increased during initial treatment, Blood urea Increased, Weight Decreased.

Rare: Diabetic ketoacidosis.

Very rare: Necrotising fasciitis of the perineum (Fournier's gangrene), Lactic acidosis, Vitamin B12 Deficiency, Liver function disorders, Hepatitis, Urticaria, Erythema, Pruritus.

Effects on ability to drive and use machines

Dapagliflozin + Metformin HCl combination has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

OVERDOSAGE

Removal of dapagliflozin by haemodialysis has not been studied. The most effective method to remove metformin and lactate is haemodialysis. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the Patient's clinical status. High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD15

Mechanism of action

Dapagliflozin + Metformin HCl combination combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Pharmacokinetics

Dapagliflozin + Metformin HCl combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride administered together as individual tablets.

Interaction with food

The administration of this medicinal product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak concentrations and a decrease in the maximum plasma concentration of 29% of dapagliflozin and 17% of metformin. These changes are not considered to be clinically meaningful.

Paediatric population

Pharmacokinetics in the paediatric population have not been studied.

The following statements reflect the pharmacokinetic properties of the individual active substances of this medicinal product.

Dapagliflozin

Absorption: Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Distribution: 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 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. 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.

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. 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 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Linearity: Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Metformin

Absorption: After an oral dose of metformin, tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/mL, even at maximum doses.

Distribution: Plasma protein binding is negligible. Metformin 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Coadministration of dapagliflozin and metformin: Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

The following statements reflect the preclinical safety data of the individual active substances of Dapagliflozin + Metformin HCl combination tablet.

Dapagliflozin: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Metformin: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

HOW SUPPLIED

Dapxiga-M Tablets 5mg/850mg: Pack of 14 Tablets
Dapxiga-M Tablets 5mg/1000mg: Pack of 14 Tablets

STORAGE

Do not store above 30°C.

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

INSTRUCTIONS

Keep away from heat, light and moisture.

Keep all medicines out of the reach of children.

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

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:
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