DAPXI-MET Tablets

(Dapagliflozin+Metformin HCl USP)

ڈیپزی۔میٹ ٹیبلیٹس

(ڈاپاگلافلوزن+میٹفارمن ہائیڈروکلورائیڈ یو ایس پی)

WARNING: LACTIC ACIDOSIS

Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, discontinue **DAPXI-MET** and hospitalize the patient immediately.

COMPOSITION:

Dapxi-Met Tablets 5mg/850mg
Each film coated tablet contains:
Dapagliflozin Propanediol Monohydrate
eq. to Dapagliflozin ..... 5mg.
Metformin Hydrochloride USP ... 850mg.
[Innovator's Specs.]

Dapxi-Met Tablets 5mg/1000mg
Each film coated tablet contains:
Dapagliflozin Propanediol Monohydrate
eq. to Dapagliflozin ..... 5mg.
Metformin Hydrochloride USP ... 1000mg.
[Innovator's Specs.]

DESCRIPTION: Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2. 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. Metformin HCl is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose.

INDICATIONS: Dapxi-Met 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.

DOSAGE AND ADMINISTRATION:

Adults with normal renal function (glomerular filtration rate [GFR] ≥90ml/min): The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of Dapagliflozin and Metformin HCl.

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 **Dapxi-Met** equivalent to Dapagliflozin 10mg, plus the total daily dose of Metformin HCl, or the nearest therapeutically appropriate dose, already being taken.

For 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 **Dapxi-Met** should receive the same daily dose of Dapagliflozin and Metformin HCl already being taken or the nearest therapeutically appropriate dose of Metformin HCl.

SPECIAL POPULATIONS:

Dosage in patients with renal impairment:

GFR ml/min	Metformin HCl	Dapagliflozin
60-89	Maximum daily dose is 3000mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 10mg.
45-59	Maximum daily dose is 2000mg. The starting dose is at most half of the maximum dose.	Dapagliflozin should not be initiated. Maximum total daily dose is 10mg.
30-44	Maximum daily dose is 1000mg. The starting dose is at most half of the maximum dose.	Dapagliflozin is not recommended.
< 30	Metformin HCl is contraindicated.	Dapagliflozin is not recommended.

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

Elderly (≥65 years): Because Metformin HCl 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 HCl-associated lactic acidosis, particularly in elderly patients. Risk of volume depletion with Dapagliflozin should also be taken into account.

Paediatric population: The safety and efficacy of Dapagliflozin in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Method of administration: Dapxi-Met should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with Metformin HCl.

CLINICAL PHARMACOLOGY: Mechanism of Action: Dapxi-Met 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 HCl, a member of the biguanide class.

PHARMACOKINETICS: Dapagliflozin:

Absorption: Dapagliflozin was rapidly and well absorbed after oral administration. Maximum Dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state Dapagliflozin C_{max} and AUC_{τ} values following once daily 10mg doses of Dapagliflozin were 158ng/ml and 628ng h/ml, respectively. The absolute oral bioavailability of Dapagliflozin following the administration of a 10mg 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 litres.

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.

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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 ($t_{1/2}$) 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 207ml/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged Dapagliflozin. After administration of a 50mg. Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.
Metformin: Absorption: After an oral dose of Metformin HCl, t_{max} is reached in 2.5 hours. 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 faeces 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. In controlled clinical trials, maximum Metformin HCl plasma levels (C_{max}) did not exceed 5µg/ml, even at maximum doses.
Distribution: Plasma protein binding is negligible. 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.
Biotransformation: Metformin HCl is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination: 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.

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 (eGFR below 30ml/min/1.73m^2).
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.

WARNINGS AND PRECAUTIONS: - Lactic acidosis - Renal function - Diabetic ketoacidosis - Urinary tract infections - Cardiac failure - Administration of iodinated contrast agents - Surgery.

PREGNANCY AND LACTATION: Pregnancy: There are no data from the use of Dapagliflozin+ Metformin HCl in pregnant women. A limited amount of data from the use of Metformin HCl in pregnant women does not indicate an increased risk of congenital malformations.
Nursing Mothers: Metformin HCl 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.

SIDE EFFECTS: Vulvovaginitis, balanitis and related genital infections: Includes, the vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis,vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.
Urinary tract infection: Includes the urinary tract infection, cystitis, Escherichia urinary tract infection, genito urinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
B_{12} Deficiency: Long-term treatment with Metformin HCl has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g. megaloblastic anaemia).
Hypersensitivity: Adverse reaction was identified through post-marketing surveillance with the use of Dapagliflozin include rash generalised, rash pruritic, rash macular, rash maculo-popular, rash pustular, rash vesicular, and rash erythematous.

DRUG 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: Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of Dapagliflozin are not altered by pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.
Metformin HCl: Concomitant use not recommended 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.
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 HCl active substance of this medicinal product.
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis: 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 HCl, close monitoring of renal function is necessary.

OVERDOSE: 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.

INSTRUCTIONS: Store below 30° C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION:
Dapxi-Met tablets 5mg/850mg are available in the pack size of 14's.
Dapxi-Met tablets 5mg/1000mg are available in the pack size of 14's.

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

PHARMA
Manufactured by:
NABIQASIM INDUSTRIES (PVT.) LTD.
17/24, Korangi Industrial Area, Karachi-Pakistan.
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