Daplyza®-MXR

ڈیپلائزا-ایم ایکس آر

[Dapagliflozin + Metformin HCl]

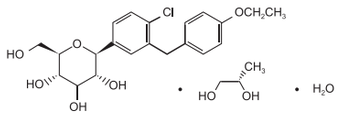
Extended-release Tablets 2.5mg + 1000mg, 5mg + 500mg, 5mg + 1000mg, 10mg + 500mg & 10mg + 1000mg

DESCRIPTION

Daplyza-M XR contains two oral anti-hyperglycemic drugs used in the management of type 2 diabetes: Dapagliflozin and Metformin HCl.

Dapagliflozin

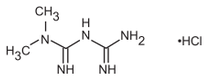
Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-,compounded with (2S)-1,2-propanediol, hydrate (1:1:1). Its molecular formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the structural formula is:



Dapagliflozin Propanediol Monohydrate

Metformin HCl

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Its molecular formula is $C_4H_{11}N_5 \cdot HCl$ and the structural formula is:



Metformin HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION

Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets is available for oral administration as:

Daplyza-M XR Tablets 2.5mg + 1000mg
Each film-coated tablet contains:
Dapagliflozin…2.5mg
Metformin HCl USP…1000mg
(as extended release)

Daplyza-M XR Tablets 5mg + 500mg
Each film-coated tablet contains:
Dapagliflozin…5mg
Metformin HCl USP…500mg
(as extended release)

Daplyza-M XR Tablets 5mg + 1000mg
Each film-coated tablet contains:
Dapagliflozin…5mg
Metformin HCl USP…1000mg
(as extended release)

Daplyza-M XR Tablets 10mg + 500mg
Each film-coated tablet contains:
Dapagliflozin…10mg
Metformin HCl USP…500mg
(as extended release)

Daplyza-M XR Tablets 10mg + 1000mg
Each film-coated tablet contains:
Dapagliflozin…10mg
Metformin HCl USP…1000mg
(as extended release)

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

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Absorption

Dapagliflozin

Following oral administration of Dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} 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 10mg dose is 78%. Administration of Dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} 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.

Metformin HCl

Following a single oral dose of Metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of Metformin absorption (as measured by AUC) from the Metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on C_{max} and T_{max} of Metformin.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metformin HCl

Distribution studies with extended-release Metformin have not been conducted; however, the apparent volume of distribution (V/F) of Metformin following single oral doses of immediate release Metformin 850mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

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-Oglucuronide accounted for 61% of a 50mg [^{14}C]-Dapagliflozin dose and is the predominant drug related component in human plasma.

Metformin HCl

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

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50mg dose of [^{14}C]-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 Dapagliflozin 10mg.

Metformin HCl

Renal clearance is approximately 3.5-times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

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 11g 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, the plasma and blood half-life of Metformin is prolonged and the renal clearance is decreased.

Patients with hepatic impairment

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of Dapagliflozin were up to 12% and 36% higher, respectively. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of Dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Elderly

Metformin HCl

Limited data from controlled pharmacokinetic studies of Metformin in healthy elderly subjects suggest that total plasma clearance of Metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in Metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Safety and effectiveness of Dapagliflozin + Metformin HCl XR Tablets have not been established in pediatric patients.

THERAPEUTIC INDICATIONS

Daplyza-M XR (Dapagliflozin + Metformin HCl) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Dapagliflozin and Metformin HCl is appropriate.

Dapagliflozin is indicated to reduce:

- The risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular (CV) risk factor.
- The risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- The risk of sustained estimated glomerular filtration rate decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

DOSAGE AND ADMINISTRATION

Prior to Initiation of Daplyza-M XR (Dapagliflozin + Metformin HCl)

- Assess renal function before initiating Daplyza-M XR (Dapagliflozin + Metformin HCl) and as clinically indicated.
- In patients with volume depletion, correct this condition before initiating Daplyza-M XR (Dapagliflozin+ Metformin HCl).

Recommended Dosing

- Take Daplyza-M XR (Dapagliflozin+ Metformin HCl) orally once daily in the morning with food.
- Swallow Daplyza-M XR (Dapagliflozin+ Metformin HCl) Tablets whole and never crush, cut, or chew. The inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet.
- Individualize the starting dose of Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets based on the patient's current regimen:
  - Patients taking an evening dose of Metformin extended-release should skip their last dose before starting Daplyza-M XR (Dapagliflozin + Metformin HCl).
  - To improve glycemic control in patients not already taking Dapagliflozin, the recommended starting dose for Dapagliflozin is 5mg once daily.
  - For indications related to heart failure and chronic kidney disease the recommended dose for Dapagliflozin is 10mg once daily.
  - Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10mg Dapagliflozin and 2000mg Metformin HCl extended-release.

Recommended Dosage in Patients with Renal Impairment

- Initiation of Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets is not recommended in patients with an eGFR between 30 to 45mL/min/1.73m^2.
- Dapagliflozin is likely to be ineffective to improve glycemic control in patients with eGFR less than 45mL/min/1.73m^2 .
- Metformin initiation is not recommended for patients with eGFR less than 45mL/min/1.73m^2 .
- No dose adjustment for Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45mL/min/1.73m^2 .
- Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets is contraindicated in patients with an eGFR below 30mL/min/1.73m^2 , end-stage renal disease, or on dialysis due to the Metformin component.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial

iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Daplyza-M XR (Dapagliflozin + Metformin HCl) if renal function is stable.

CONTRAINDICATIONS

The combination of Dapagliflozin + Metformin HCl XR Tablets is contraindicated in:

- Patients with hypersensitivity to Dapagliflozin, Metformin HCl or to any excipient of the product.
- Severe renal impairment (eGFR below 30mL/min/1.73m^2), end-stage renal disease or patients on dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
- Hepatic impairment.
- Diabetic pre-coma.
- Acute conditions with the potential to alter renal function such a dehydration, severe infection, and shock.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, and recent myocardial infarction.
- Acute alcohol intoxication and alcoholism.

ADVERSE REACTIONS

Following adverse reactions have been reported with the use of Dapagliflozin + Metformin HCl XR Tablets:

Very Common

Hypoglycemia (when used with SU or insulin), and gastrointestinal symptoms.

Common

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

Uncommon

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

Rare

Diabetic ketoacidosis.

Very Rare

Necrotizing fasciitis of the perineum (Fournier's gangrene), lactic acidosis, vitamin B_{12} deficiency, liver function disorders, hepatitis urticarial, erythema and pruritus.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

PRECAUTIONS

WARNING: LACTIC ACIDOSIS

Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of Metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and Metformin plasma levels generally >5mcg/mL.

Risk factors for Metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

If Metformin-associated lactic acidosis is suspected, immediately discontinue Dapagliflozin + Metformin HCl XR Tablets. Prompt hemodialysis is recommended.

Lactic Acidosis

There have been post-marketing cases of Metformin-associated lactic acidosis, including fatal cases. If Metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Dapagliflozin + Metformin HCl XR Tablets.

Volume Depletion

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. Patients with impaired renal function (eGFR less than 60mL/min/1.73m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Dapagliflozin + Metformin HCl XR Tablets in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Dapagliflozin + Metformin HCl XR Tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co-transporter 2 (SGLT2) inhibitors, including Dapagliflozin. If ketoacidosis is suspected, Dapagliflozin + Metformin HCl XR Tablets should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement. Before initiating Dapagliflozin + Metformin HCl XR Tablets, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin + Metformin HCl XR Tablets for at least 3 days prior to surgery. Consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin + Metformin HCl XR Tablets in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Dapagliflozin + Metformin HCl XR Tablets.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Dapagliflozin. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Dapagliflozin + Metformin HCl XR Tablets may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogues. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Dapagliflozin + Metformin HCl XR Tablets.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in in patients with diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with Dapagliflozin + Metformin HCl XR Tablets presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Dapagliflozin + Metformin HCl XR Tablets closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Dapagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Vitamin B_{12} Deficiency

Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.

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.

Effects on ability to drive and use machines

Combination of Dapagliflozin + Metformin HCl XR Tablets 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.

Pregnancy

Dapagliflozin + Metformin HCl XR Tablets is not recommended during the second and third trimesters of pregnancy. Advise females of the potential risk to a fetus especially during the second and third trimesters.

Nursing Mothers

Dapagliflozin + Metformin HCl XR Tablets is not recommended when breastfeeding.

DRUG INTERACTIONS

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Dapagliflozin + Metformin HCl XR Tablets may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of Metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to Metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin + Metformin HCl XR Tablets.

Insulin or Insulin Secretagogues

The risk of hypoglycemia may be increased when Dapagliflozin + Metformin HCl is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea). Concomitant use may require lower doses of insulin or the insulin secretagogues to reduce the risk of hypoglycemia.

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Dapagliflozin + Metformin HCl XR Tablets, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Dapagliflozin + Metformin HCl XR Tablets, observe the patient closely for hypoglycemia.

Lithium

Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during Dapagliflozin + Metformin HCl XR Tablets, initiation and dosage changes.

Positive Urine Glucose Test

SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

Diuretics

This medicinal product may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

OVERDOSAGE

Dapagliflozin

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

Metformin HCl

Overdose of Metformin HCl has occurred, including ingestion of amounts >50 grams. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases. Metformin is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdosage is suspected.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

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

HOW SUPPLIED

Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets 2.5mg + 1000mg is available in pack of 14's.
Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets 5mg + 500mg is available in pack of 14's.
Daplyza-M XR (Dapagliflozin + Metformin HCl) Tablets 5mg + 1000mg is available in pack of 14's.
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Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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PAK-200017049