Dapxiga-M XR

4000002962

(Dapagliflozin and Metformin HCl Extended Release Tablets)

Product Specifications: Innovator

Dapxiga-M XR Tablets 2.5 mg/1000 mg: Each film coated bi-layered tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin ..... 2.5 mg (as Immediate Release Layer)
Metformin Hydrochloride U.S.P. ..... 1000 mg (as Extended-Release Layer)

Dapxiga-M XR Tablets 5 mg/500 mg: Each film coated bi-layered tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin ..... 5 mg (as Immediate Release Layer)
Metformin Hydrochloride U.S.P. ..... 500 mg (as Extended-Release Layer)

Dapxiga-M XR Tablets 5 mg/1000 mg: Each film coated bi-layered tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin ..... 5 mg (as Immediate Release Layer)
Metformin Hydrochloride U.S.P. ..... 1000 mg (as Extended-Release Layer)

Dapxiga-M XR Tablets 10 mg/500 mg: Each film coated bi-layered tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin ..... 10 mg (as Immediate Release Layer)
Metformin Hydrochloride U.S.P. ..... 500 mg (as Extended-Release Layer)

Dapxiga-M XR Tablets 10 mg/1000 mg: Each film coated bi-layered tablet contains:
Dapagliflozin Propanediol Monohydrate U.S.P. eq. to Dapagliflozin ..... 10 mg (as Immediate Release Layer)
Metformin Hydrochloride U.S.P. ..... 1000 mg (as Extended-Release Layer)

WARNING: LACTIC ACIDOSIS

Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant brady arrhythmias. 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 (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/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.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information (see Dosage and Administration, Contraindications, Warnings and Precautions, Drug Interactions, and Use in Specific Populations)

If metformin-associated lactic acidosis is suspected, immediately discontinue Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION

Dapxiga-M XR tablets contain: dapagliflozin, a SGLT2 inhibitor, and metformin HCl, a biguanide.

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). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the formula weight is 502.98.

Metformin hydrochloride: Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63.

CLINICAL PARTICULARS

Therapeutic indications

Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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.
- 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.

Limitations of Use

- Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus
- Because of the metformin component, the use of Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is limited to adults with type 2 diabetes mellitus for all indications.
- Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is not expected to be effective in these populations.

Posology and method of administration

Prior to Initiation of Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release)

The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.

- Assess renal function before initiating Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) therapy and periodically thereafter. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- Assess volume status. In patients with volume depletion, correct this condition before initiating Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release)

Recommended Dosage

- Individualize the starting dose of Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) based upon the patient's current regimen. Patients taking an evening dose of metformin extended-release should skip their last dose before starting Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release)
- To improve glycemic control in patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily.
- For indications related to heart failure and chronic kidney disease the recommended dose for dapagliflozin is 10 mg once daily.
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2,000 mg metformin hydrochloride (HCl) extended-release.

Patients with Renal Impairment

- No dose adjustment for Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m2.
- Initiation of Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m2. Assess the benefit and risk of continuing therapy if eGFR falls persistently below this level.
  - Dapagliflozin is likely to be ineffective to improve glycemic control in patients with eGFR less than 45 mL/min/1.73 m2.
  - Metformin initiation is not recommended for patients with eGFR less than 45 mL/min/1.73 m2.
- Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) is contraindicated in patients with an eGFR below 30 mL/min/1.73 m2, end-stage renal disease, or on dialysis due to the metformin component.

Discontinuation for Iodinated Contrast Imaging Procedures

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Discontinue Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) 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 Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) if renal function is stable.

Temporary Interruption for Surgery

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Withhold Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) when the patient is clinically stable and has resumed oral intake.

Method of Administration:

- Take Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) orally once daily in the morning with food.
- Swallow Dapxiga-M XR (Dapagliflozin and Metformin hydrochloride extended-release) tablets whole and never crush, cut, or chew.

Contraindication

Dapagliflozin and Metformin hydrochloride extended-release combination is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m2), end-stage renal disease or patients on dialysis.
- History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to metformin HCl.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS AND PRECAUTIONS

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 and Metformin hydrochloride extended-release combination.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Drug Interactions: The concomitant use of Dapagliflozin and Metformin hydrochloride extended-release combination with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs). Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Hypoxic States: Several of the post-marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Dapagliflozin and Metformin hydrochloride extended-release combination.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Dapagliflozin and Metformin hydrochloride extended-release combination.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Dapagliflozin and Metformin hydrochloride extended-release combination.

in patients with clinical or laboratory evidence of hepatic disease.

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis: In patients with type 1 diabetes mellitus, dapagliflozin, a component of Dapagliflozin and Metformin hydrochloride extended-release combination, significantly increases the risk of diabetic ketoacidosis. Type 2 diabetes mellitus and pancreatic disorders are also risk factors for ketoacidosis. There have been post-marketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including dapagliflozin.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. If ketoacidosis is suspected, discontinue Dapagliflozin and Metformin hydrochloride extended-release combination. Monitor patients for resolution of ketoacidosis before restarting Dapagliflozin and Metformin hydrochloride extended-release combination. Withhold Dapagliflozin and Metformin hydrochloride extended-release combination, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume Dapagliflozin and Metformin hydrochloride extended-release combination when the patient is clinically stable and has resumed oral intake.

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 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Dapagliflozin and Metformin hydrochloride extended-release combination in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension and renal function after initiating therapy.

Urosepsis and Pyelonephritis: Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), have been identified in post-marketing surveillance in patients with diabetes mellitus

receiving SGLT2 inhibitors, including dapagliflozin. Discontinue Dapagliflozin and Metformin hydrochloride extended-release combination, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Vitamin B12 Concentrations: In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to 3-year intervals in patients on Dapagliflozin and Metformin hydrochloride extended-release combination and manage any abnormalities.

Genital Mycotic Infections: Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data showing adverse renal effects, Dapagliflozin and Metformin hydrochloride extended-release combination is not recommended during the second and third trimesters of pregnancy. Limited data with Dapagliflozin and Metformin hydrochloride extended-release combination or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Lactation: There is no information regarding the presence of Dapagliflozin and Metformin hydrochloride extended-release combination or dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk. Dapagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin and Metformin hydrochloride extended-release combination is not recommended while breastfeeding.

Females and Males of Reproductive Potential: Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use: Safety and effectiveness of Dapagliflozin and Metformin hydrochloride extended-release combination in pediatric patients under 18 years of age have not been established.

Geriatric Use: No Dapagliflozin and Metformin hydrochloride extended-release combination dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Hepatic Impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Dapagliflozin and Metformin hydrochloride extended-release combination is not recommended in patients with hepatic impairment

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 and Metformin hydrochloride extended-release combination may increase the risk for lactic acidosis.

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

Alcohol: Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Insulin or Insulin Secretagogues: The risk of hypoglycemia may be increased when Dapagliflozin and Metformin hydrochloride extended-release combination is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea)

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, sympathomimetics, calcium channel blocking drugs, and isoniazid.

Lithium: Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

Positive Urine Glucose Test: SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

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.

Adverse Reactions

Lactic Acidosis, Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis, Volume Depletion, Urosepsis and Pyelonephritis, Use with Medications Known to Cause Hypoglycemia, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), Vitamin B12 Concentrations, Genital Mycotic Infections.

Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin: Female genital mycotic infections, Nasopharyngitis, Urinary tract infections, Diarrhea, Headache, Male genital mycotic infections, Influenza, Nausea, Back pain, Dizziness, Cough, Constipation, Dyslipidemia, Pharyngitis, Increased urination, Discomfort with urination.

Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with Dapagliflozin: Female genital mycotic infections, Nasopharyngitis, Urinary tract infections, back pain, increased urination, male genital mycotic infections, Nausea, Influenza, Dyslipidemia, Constipation, Discomfort with urination, pain in extremity. Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment.

Laboratory Tests: In clinical studies following has been reported in dapagliflozin treated patients: Increases in Serum Creatinine and Decreases in eGFR, Increase in Hematocrit, Increase in Low-Density Lipoprotein Cholesterol.

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

Post-marketing Experience: Dapagliflozin: Necrotizing fasciitis of the perineum (Fournier's Gangrene), urosepsis and pyelonephritis, Ketoacidosis Acute kidney injury, Rash. Metformin HCl: Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

OVERDOSAGE

Dapagliflozin: The removal of dapagliflozin by hemodialysis has not been studied.

Metformin HCl: Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Dapagliflozin: Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose, and thereby promotes 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. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics

Dapagliflozin and Metformin hydrochloride extended-release combination:

The administration of Dapagliflozin and Metformin hydrochloride extended-release combination in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Food has no relevant effect on the pharmacokinetics of metformin when administered as Dapagliflozin and Metformin hydrochloride extended-release combination tablets.

Absorption: Dapagliflozin: Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Metformin HCl: Following a single oral dose of metformin extended-release, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours.

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 850 mg 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 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin HCl: Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination: Dapagliflozin: Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg 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 (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin and Metformin hydrochloride extended-release combination:

No animal studies have been conducted with Dapagliflozin and Metformin hydrochloride extended-release combination to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

Dapagliflozin: Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats.

Metformin HCl: No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. There was no evidence of a mutagenic potential of metformin in the vitro tests. Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3-times the maximum recommended human dose based on body surface area comparisons.

HOW SUPPLIED

Dapxiga-M XR Tablets 2.5mg/1000mg:	Pack of 14 Tablets
Dapxiga-M XR Tablets 5mg/500mg:	Pack of 14 Tablets
Dapxiga-M XR Tablets 5mg/1000mg:	Pack of 14 Tablets
Dapxiga-M XR Tablets 10mg/500mg:	Pack of 14 Tablets
Dapxiga-M XR Tablets 10mg/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:

FEROZSONS LABORATORIES LIMITED

P. O. Ferozsons, Nowshera-Pakistan

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