120x320mm

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Daplozmet XR®

(Dapagliflozin + Metformin HCl Extended Release)

Highnoon

COMPOSITION

Daplozmet XR 5mg/500mg Tablet: Each bi-layered film-coated tablet contains: Dapagliflozin as Propanediol Monohydrate (immediate release) 5mg
Metformin HCl (extended release) 500mg

Daplozmet XR 5mg/1000mg Tablet: Each bi-layered film-coated tablet contains: Dapagliflozin as Propanediol Monohydrate (immediate release) 5mg
Metformin HCl (extended release) 1000mg

Daplozmet XR 10mg/500mg Tablet: Each bi-layered film-coated tablet contains: Dapagliflozin as Propanediol Monohydrate (immediate release) 10mg
Metformin HCl (extended release) 500mg

Daplozmet XR 10mg/1000mg Tablet: Each bi-layered film-coated tablet contains: Dapagliflozin as Propanediol Monohydrate (immediate release) 10mg
Metformin HCl (extended release) 1000mg

DESCRIPTION

It contains dapagliflozin, a SGLT2 inhibitor, and metformin HCl, a biguanide.

MECHANISM OF ACTION

Dapagliflozin

Dapagliflozin is an inhibitor of the SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, Dapagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. It 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

Metformin is a biguanide with antihyperglycemic effects, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin decreases hepatic glucose production by inhibiting gluconeogenesis, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

Dapagliflozin

Peak plasma concentrations of dapagliflozin occur within two to three hours after an oral dose, with a bioavailability of about 78 %. It is about 91 % bound to the plasma proteins. Dapagliflozin is extensively metabolized to inactive metabolites via uridine diphosphate glucuronosyltransferase (UGT1A9) in the liver and kidney. It has a plasma terminal half-life of about 13 hours. About 75 % of the dose is excreted in the urine and 21% in the faeces.

Metformin

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Protein binding in plasma is negligible. Metformin is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS AND USAGE

It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- 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.

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.

However, It is not recommended for use to improve glycaemic control in patients with type 1 diabetes mellitus. Because of the metformin component, its use is limited to adults with type 2 diabetes mellitus for all indications. It 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.

DOSAGE AND ADMINISTRATION

Assessment of renal function and volume status is recommended before initiating treatment with this combination. Volume depletion should be rectified prior to starting therapy. Take orally once daily in the morning with food. Swallow tablets whole and do not crush, cut, or chew. Individualize the starting dose of based upon the patient's current regimen. Patients taking an evening dose of metformin extended release should skip their last dose before starting this combination.

- To improve glycaemic 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 2,000mg metformin hydrochloride (HCl) extended release.

No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m². Initiation 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 glycaemic 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.

Withhold for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume when the patient is clinically stable and has resumed oral intake.

Discontinue 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 if renal function is stable.

CONTRAINDICATIONS

It 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.
- 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.
- Hypersensitivity to the active substances or to any of the excipients.

ADVERSE REACTIONS

The reported adverse events are; lactic acidosis, diabetic ketoacidosis, ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia (when used with SU or insulin), necrotizing fasciitis of the perineum (Fournier's Gangrene), vitamin B12 deficiency, genital mycotic infections, female genital mycotic infections (vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, vaginitis bacterial, vulvitis, genitourinary tract infection), nasopharyngitis, urinary tract infections (cystitis, pyelonephritis, urethritis, prostatitis, Escherichia urinary tract infection, genitourinary tract infection, , trigonitis, kidney infection), diarrhoea, headache, male genital mycotic infections (balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, balanoposthitis, penile infection), influenza, nausea, back pain, dizziness, cough, constipation, pharyngitis, dyslipidaemia, increase urination (pollakiuria, polyuria, urine output increased), discomfort with urination, hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity), , acute kidney injury, cholestatic and hepatocellular injury, mixed hepatocellular injury, dehydration, hypovolaemia, hypotension, thirst, dry mouth, dysuria, nocturia, taste disturbance, decrease weight liver function disorders, hepatitis, rash, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, rash erythematous, urticaria, erythema, pruritus, pruritus genital, serum creatinine increase, decrease in eGFR, haematocrit increase, low density lipoprotein cholesterol increase, creatinine renal clearance decreased during initial treatment, blood creatinine increased during initial treatment and blood urea increased.

DRUG INTERACTIONS

- 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 may increase the risk for lactic acidosis.
- 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 is known to potentiate the effect of metformin on lactate metabolism.
- The risk of hypoglycaemia may be increased when concomitantly used with insulin or insulin secretagogues (e.g., sulfonylurea).
- Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
- 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.
- Measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors.

WARNINGS AND PRECAUTIONS

- Cases of metformin-associated lactic acidosis, including fatal cases were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of this combination (dapagliflozin and metformin) treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt haemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Haemodialysis has often resulted in reversal of symptoms and recovery.
- 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. Before initiating treatment with this combination (dapagliflozin and metformin), obtain an estimated glomerular filtration rate (eGFR). It is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m². Obtain an eGFR at least annually in patients. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- The concomitant use of this combination (dapagliflozin and metformin) 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.
- 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.
- 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. Stop this combination (dapagliflozin and metformin) at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart this combination (dapagliflozin and metformin) if renal function is stable.
- Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment.
- This combination (dapagliflozin and metformin) should be temporarily discontinued while patients have restricted food and fluid intake.
- 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 azotaemia. When such events occur, discontinue this combination (dapagliflozin and metformin).
- 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 this combination (dapagliflozin and metformin).
- Patients with hepatic impairment have developed with cases of metforminassociated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid its use in patients with clinical or laboratory evidence of hepatic disease.
- In patients with type 1 diabetes mellitus, dapagliflozin, significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. This combination (dapagliflozin and metformin) is not indicated for glycaemic control in patients with type 1 diabetes mellitus. Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including dapagliflozin. Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse. Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing this combination (dapagliflozin and metformin); however, there have been reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors. Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue this combination (dapagliflozin and metformin), promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting it. Withhold this combination, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume it when the patient is clinically stable and has resumed oral intake.
- Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. 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 treatment 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.
- 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. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.
- Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycaemia. Hence there may be increase in the risk of hypoglycaemia 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 hypoglycaemia when used in combination with this combination (dapagliflozin and metformin).
- Reports of 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 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 this combination (dapagliflozin and metformin) 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 this combination (dapagliflozin and metformin), closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.
- A decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, have been observed with metformin. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anaemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 years intervals in patients on this combination and manage any abnormalities.
- 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.
- An increase in cases of lower limb amputation (primarily of the toe) has been observed 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.
- Due to its mechanism of action, patients taking this medicinal product (dapagliflozin and metformin) will test positive for glucose in their urine.

USE IN SPECIFIC POPULATIONS

Pregnancy

It is not recommended during the second and third trimesters of pregnancy. Limited data in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There does not seem to be a clear association with metformin and major birth defects, miscarriage, or adverse maternal or foetal outcomes when metformin was used during pregnancy.

Lactation

There is no information regarding the presence of this 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, however, there is insufficient information on the effects of metformin on the breastfed infant. 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 this combination is not recommended while breastfeeding.

Fertility

There is a potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Elderly

No dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients. However, Elderly (≥ 65 years) 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.

Paediatric population

Safety and effectiveness of this combination in paediatric patients under 18 years of age have not been established.

Renal Impairment

Initiation of this combination (dapagliflozin and metformin) is not recommended in patients with an eGFR below 45 mL/min/1.73 m² and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease or patients on dialysis. Patients with diabetes and renal impairment using dapagliflozin 10mg are more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. Use of dapagliflozin 10mg for glycaemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m².

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. This combination (dapagliflozin and metformin) is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m².

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. This combination (dapagliflozin and metformin) is not recommended in patients with hepatic impairment.

OVERDOSAGE

The removal of dapagliflozin by haemodialysis has not been studied. Overdose of metformin HCl has occurred, including ingestion of amounts >50 grams. Lactic acidosis has been reported. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE & INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from light.

PRESENTATION

Daplozmet XR 5/500mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Daplozmet XR 5/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Daplozmet XR 10/500mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Daplozmet XR 10/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

ڈیپلوزمیٹ ایکس آر®

(ڈیپاگلیفلوزن + میٹ فارمن ہائیڈروکلورائیڈ ایکسٹینڈیڈ ریلیز)

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بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
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