Diajard-MXR™

(Empagliflozin + Metformin HCl)

Highnoon

COMPOSITION

Diajard-MXR 5mg/1000mg Tablet:
Each film-coated tablet contains:
Empagliflozin (as immediate-release layer) 5mg
Metformin HCl (as extended-release layer) 1000mg

Diajard-MXR 10mg/1000mg Tablet:
Each film-coated tablet contains:
Empagliflozin (as immediate-release layer) 10mg
Metformin HCl (as extended-release layer) 1000mg

Diajard-MXR 12.5mg/1000mg Tablet:
Each film-coated tablet contains:
Empagliflozin (as immediate-release layer) 12.5mg
Metformin HCl (as extended-release layer) 1000mg

Diajard-MXR 25mg/1000mg tablet:
Each film-coated tablet contains:
Empagliflozin (as immediate-release layer) 25mg
Metformin HCl (as extended-release layer) 1000mg

DESCRIPTION

Diajard-MXR (empagliflozin and metformin hydrochloride extended release) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and metformin hydrochloride.
Empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) and metformin, a member of the biguanide class.

MECHANISM OF ACTION

Empagliflozin
Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increased urinary glucose excretion.

Metformin
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS

No change in overall exposure of empagliflozin is expected when empagliflozin and metformin extended is administered with food.
For metformin hydrochloride extended-release high-fat meals may increase systemic exposure to metformin (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while Cmax may not be affected. Meals could prolonged Tmax by approximately 3 hours.

Empagliflozin
After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Plasma protein binding was 86.2%. No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates. The primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours. The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug. It may be administered with or without food.

Metformin
Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; Following a single oral dose of metformin hydrochloride extended-release after a meal, the time to reach maximum plasma metformin concentration (Tmax) may be achieved at approximately 7 to 8 hours, providing equivalent systemic exposure, as measured by AUC, and up to 35% higher Cmax of metformin relative to the immediate-release.
Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax may not affected. 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 hour. Metformin crosses the placenta and is distributed into the breast milk in small amounts.

INDICATIONS AND USAGE

It is indicated:

- An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus with both empagliflozin and metformin hydrochloride is appropriate.
- It is not recommended in patients with eGFR less than 45 mL/min/1.73 m², due to Metformin component. It is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² or in patients on dialysis.
- Reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

It is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients

Limitations of Use

It is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

It is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m². It is likely to be ineffective in this setting based upon its mechanism of action

DOSAGE AND ADMINISTRATION

In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating this combination (Empagliflozin and Metformin HCl). Assess renal function before initiating this combination (Empagliflozin and Metformin HCl) and on clinically indicated.

- Individualize the starting dose of Diajard-MXR (Empagliflozin and Metformin HCl) based on the patient's current regimen:
  - In patients on metformin hydrochloride, switch to Diajard-MXR (Empagliflozin and Metformin HCl) containing a similar total daily dose of metformin hydrochloride and a total daily dose of empagliflozin 10 mg.
  - In patients on empagliflozin, switch to Diajard-MXR (Empagliflozin and Metformin HCl) containing the same total daily dose of empagliflozin and a total daily dose of metformin hydrochloride extended-release 1000 mg.
  - In patients already treated with empagliflozin and metformin hydrochloride, switch to Diajard-MXR (Empagliflozin and Metformin HCl) containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride.

Take Diajard-MXR (Empagliflozin and Metformin HCl) orally once daily with a meal in the morning.
Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000mg and empagliflozin 25mg. The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride. Diajard-MXR (Empagliflozin and Metformin HCl) 10mg/1000mg and 25mg/1000mg tablets should be taken as a single tablet once daily. Diajard-MXR (Empagliflozin and Metformin HCl) 5mg/1000mg and 12.5mg/1000mg tablets should be taken as two tablets together once daily.

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same time. In that case, the missed dose should be skipped.

CONTRAINDICATIONS

It is contraindicated in patients with:

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients.

ADVERSE REACTIONS

The reported adverse events are; lactic acidosis, hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, thirst, taste, gastrointestinal symptoms,, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (fournier's gangrene), genital mycotic infections, hypersensitivity reactions, increased low-density lipoprotein cholesterol, vitamin B12 deficiency, urinary tract infection (asymptomatic bacteriuria, cystitis), female genital mycotic infection (vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial), increased urination (polyuria, pollakiuria, nocturia), upper respiratory tract infection, dyslipidemia, arthralgia, male genital mycotic infections (balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection), nausea, volume depletion (blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, syncope), increase urination (e.g., polyuria, pollakiuria, and nocturia), increase in serum creatinine, decreases in eGFR, phimosis, hypoglycemia, increase hematocrit, angioedema, skin reaction (rash, urticaria), pruritus generalized, nasopharyngitis, diarrhea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, headache, cholestatic, hepatocellular, thirst, constipation, gastrointestinal symptoms, and mixed hepatocellular liver injury.

DRUG INTERACTIONS

- Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
- Coadministration of this combination (Empagliflozin and Metformin HCl) with an Insulin secretagogues (e.g. sulfonylurea) or Insulin may require lower doses of Insulin secretagogues or Insulin to reduce the risk of hypoglycemia.
- Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
- Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- 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 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.
- 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 of lactic acidosis. Consider more frequent monitoring of these patients.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving empagliflozin and metformin, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving empagliflozin and metformin, the patient should be observed closely for hypoglycemia.
- Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving empagliflozin and metformin.
- Concomitant use of SGLT2 inhibitors with Lithium may decrease serum Lithium concentration. Monitor serum Lithium concentration more frequently during initiation of this combination (Empagliflozin and Metformin HCl) and during changes.

WARNINGS AND PRECAUTIONS

Lactic Acidosis

There have been reported cases of metformin-associated lactic acidosis, including fatal cases. Malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis.

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, along with immediate discontinuation of drug is recommended. Prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. Hemodialysis has often resulted in reversal of symptoms and recovery.

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:

Renal Impairment: The 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 this combination (Empagliflozin and Metformin HCl), obtain an estimated glomerular filtration rate (eGFR). It is contraindicated in patients with an eGFR below 30 mL/min/1.73 m². Obtain an eGFR at least annually in all patients taking (Empagliflozin and Metformin HCl) combination. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of the combination (Empagliflozin and Metformin HCl) with specific drugs may increase the risk of metformin-associated lactic acidosis. 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 patient.

Radiological Studies with Contrast: 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 (Empagliflozin and Metformin HCl) combination at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60mL/min/1.73 m²; 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 (Empagliflozin and Metformin HCl) combination, if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. It should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia).

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 (Empagliflozin and Metformin HCl) combination.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated 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.

Volume Depletion

Empagliflozin causes 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. Symptomatic hypotension may occur after initiating particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating, assess for volume contraction and correct volume status is indicated. Monitor for signs and symptoms of hypotension after initiating therapy. Consider interrupting treatment if volume depletion occurs.

Ketoacidosis

Ketoacidosis, have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. It is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with empagliflozin and metformin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with empagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, it should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. Before initiating, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with empagliflozin and metformin consider monitoring for ketoacidosis and temporarily discontinuing (Empagliflozin and Metformin HCl) combination in situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Urosepsis and Pyelonephritis

Urosepsis and pyelonephritis have been reported in patients receiving SGLT2 inhibitors, including empagliflozin. 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.

Hypoglycemia with Concomitant use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.
Hypoglycemia does not occur in patients receiving metformin alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as Sulphonyl urea and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs. Monitor for a need to lower the dose of it, to minimize the risk of hypoglycemia in these patients.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males.
Patients treated with empagliflozin 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 it, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Empagliflozin 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.

Hypersensitivity Reactions

Hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue empagliflozin; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Vitamin B_{12} Levels

A decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex. This risk may be more relevant to patients receiving long-term treatment with metformin. The decrease in vitamin B12 levels appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on it and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurement at 2 to 3 year intervals may be useful.

USE IN SPECIFIC POPULATIONS

Pregnancy

It is not recommended during the second and third trimesters of pregnancy. Limited data available with empagliflozin in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Lactation

There is no information regarding the presence of empagliflozin in human milk, the effects of empagliflozin on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise women that use of empagliflozin 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

The safety and effectiveness of this combination (Empagliflozin and Metformin HCl) in pediatric patients under 18 years of age have not been established.

Geriatric Use

Renal function abnormalities can occur after initiating empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.
No empagliflozin dosage change is recommended based on age. Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions and urinary tract infection increased in patients who were 75 years of age and older.
Metformin dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

It should not be initiated in patients with eGFR less than 45 mL/min/1.73 m². The metformin component is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) end stage renal diseases. The glucose lowering benefits of Empagliflozin 25mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.
Empagliflozin and metformin combination should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m² due to the metformin component and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end-stage renal disease, or dialysis.

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

Hepatic Impairment

Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. It is not recommended in patients with hepatic impairment.

OVERDOSAGE

In the event of an overdose with empagliflozin, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Hemodialysis may be useful partly for removal of accumulated metformin from patients in whom overdosage is suspected.

DOSAGE AND 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 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Diajard-MXR 5mg/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Diajard-MXR 10mg/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Diajard-MXR 12.5mg/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Diajard-MXR 25mg/1000mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

ڈائیاجارڈ-ایم ایکس آر™

(ایمپاگلیفلوزن + میٹ فارمن ہائیڈروکلورائیڈ)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
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www.highnoon-labs.com

Item Code No. 14002877