Diajard-M™

(Empagliflozin + Metformin HCI)



COMPOSITION
Diajard-M 5mg/500mg Tablet:
Each film-coated tablet contains: Empagliflozin 5mg
Metformin HCI 500mg
Diajard-M 12.5mg/500mg Tablet:
Each film-coated tablet contains: Empagliflozin 12.5mg

Metformin HCI 500mg Diajard-M 5mg/1000mg Tablet:

Each film-coated tablet contains: Empagliflozin 5mg

Metformin HCI 1000mg

Diajard-M 12.5mg/1000mg Tablet:
Each film-coated tablet contains: Empagliflozin 12.5mg

Metformin HCI 1000ma

DESCRIPTION

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Diajard-M 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 uninary glucose excretion.

Metformin
Metformin is an antihyperglucomic agent which improves glucose.

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.

PHARMACONITETICS

Empagiliflozin

After oral administration, peak plasma concentrations of empagiliflozin were reached at 1.5 hours post-dose. Plasma concentrations declined in a biphasic manner with a rapid distribution phase and are relatively slow terminal phase. Plasma protein binding was 86.2%. No major metabolites of empagiliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates. The primary route of metabolism of empagiliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT17A8, and UGT17A8. The paperent terminal elimination half-life of empagiliflozin 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 hydrochloride is slowly and incompletely absorbed from

drug. It may be administered with or without food. Metformin Mydrochloride 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:

 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.
- metformin in combination with other antidiabetic drugs or
- Reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular

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 in patients with eGFR less than 45 mL/min/1.73m², due to Metformin component. It is contraindicated in patients with an eGFR less than 30 mL/min/1.73m² or in

DOSAGE AND ADMINISTRATION
In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating Diajard-M (empagliflozin and metformin).

- Individualize the starting dose of Diajard-M (empagliflozin and metformin) based on the patient's current regime
- tormin) based on the patients current regimen:
 In patients on metformin hydrochloride, switch to
 (empagliflozin and metformin) combination containing
 empagliflozin 5 mg with a similar total daily dose of
 metformin hydrochloride.
 In patients on empagliflozin, switch to (empagliflozin and
 metformin) combination, containing metformin
 hydrochloride 500 mg with a similar total daily dose of
 empagliflozin
- impaglificzin.

 In patients already treated with empaglificzin and metformin hydrochloride, switch to combination (empaglificzin and metformin) containing the same total daily doses of each component.

Take Diajard-M (empagliflozin and metformin) twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000mg and empagliflozin 25mg.

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

CONTRAINDICATIONS

- CON IRAINDICA ITONS
 It is contraindicated in patients with:
 Severe renal impairment (eGFR less than 30 mL/min/1.73m²), 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.
 Diabetic pre-coma.

ADVERSE REACTIONS

The reported adverse events are; lactic acidosis, hypotension, ketoacidosis, acute kidney injury and impairment in renaf function, urosepsis and pyelonephritis, thirst, gastrointestinal symptoms, serum lipids increased, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fascitis of the perineum (Fournier's gangrene), genital mycotic infections, hypersensitivity reactions, increased low-density lipoprotein cholesterol, vitamin B12 deficiency, urinary tract infection claymptomatic bacteriuria, cystitis), female genital mycotic infection (vulvovaginal mycotic infection, vaginal infection, villitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection, genital candidiasis, genital infection, genital infection, dyslipidemia, arthratigia, male genital mycotic infections (balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candidas, sorolal abscess, penile infection), nausea, volume depletion (blood pressure systotic decreased, nausea, volume depletion (blood pressure systolic decreased, dehydration, hypotension, hypovelemia, orthostatic hypotension, syncope), increase urination (e.g., polyuria, pollakiuria, and nocturia), increase in serum creatinine, decreases in eGFR. phimosis, hypoglycemia, increase hematocrit, angioedema, skir reaction (rash, urticaria), pruritus generalized, nasopharyngilis, diarrhea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, headache, cholestatic, hepatocellular, constipation, and mixed hepatocellular liver injury.

- RUG 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 empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

 Co-administration of this combination (Empagliflozin and Metformin) with an Insulin secretagogue (e.g. sulphonylurea) or Insulin may require lower doses of this Insulin secretagogue 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 transport-e/ [OCT2] / multifurg and toxin extrusion inhibitors such as ranolazine, vandetanib, dottlegravir, 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
- 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, phenothazines, thyroid products, estrogens, oral contraceptives, phenothazines, thyroid products, estrogens, oral contraceptives, phenothazines, thyroid products, when such drugs are administered to a patient receiving empagliflozin and metformin, the patient should be dosely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving empagliflozin and metformin, the patient should be observed dosely for hypoglycemia.

 Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohor 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) and during changes.

WARNINGS AND PRECAUTIONS

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 bradyarrhythmia's 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 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 reprovided 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

renal impairment because measurements assume the kidney.

Before initiating this combination (empagliflozin and metformin), 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 this combination (empagliflozin and metformin). In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

empagliflozin and metformin) 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 this combination (empagliflozin and metformin) at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73m²; 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) combinatio

<u>Surgery and Other Procedures:</u> 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).

when accompanied by hypopertusion 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 this combination (Empagliflozin and Metformin HCI).

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 this combination (Empagliflozin and Metformin HCI) use in patients with clinical or laboratory evidence of hepatic disease.

Volume Depletion

Volume Depletion
Empagliflozi, 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 her mal impairment, the elderly, in patients with how systolic blood pressure, and in patients on diuretics. Before initiating, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy. Consider interrupting treatment if volume depletion occurs.

Consider interrupting treatment it volume depletion occurs.

Ketoacidosis
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. should be evaluated, and prompt treatment should be instituted Freatment of ketoacidosis may require insulue. Treatment of ketoacidosis may require insulue, fluid and carbohydrate replacement. Before initiating, conside 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 empagifiliozin and and alcohol abuse. In patients treated with empagliflozin and metformin consider monitoring for ketoacidosis and temporarily discontinuing the combination (empagliflozin and metformin) in situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Before initiating this combination (Empagliflozin and Metformin) consider factors in the natient history that may predispose to

- 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 are under scheduled surgery, conside
- For patients who are under scheduled surgery, consider temporarily discontinuing this combination (Empagliflozin and Metformin) for at least 3 days prior to surgery.

 Consider monitoring for ketoacidosis in temporarily discontinue this combination (Empagliflozin and Metformin) 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 this combination (Empagliflozin and Metformin).

 Educate patient on the signs and symptoms of ketoacidosis and instruct patients to discontinue this combination (Empagliflozin and Metformin) and seek medical attention immediately if signs and symptoms occur.

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 with Concomitant use with insurin and insurin 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)

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) Reports of necrolizing fasciitis of the perineum (Fournier's garnen), a rare but serious and life-threatening necrotizing infection have been reported in patients with diabetes mellitus receiving Fottler inhibitors, including empaglificzin. 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 along with level or initiatises, shound be assessed to inevitating fascilits. 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
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

Vitamin B12 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 empagififozin 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 process that use of empagliflozin is not recommended while women that use of empagliflozin is not recommended while breastfeeding.

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

Geriatric Use

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 elderty 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. elderly patients.

Renal Impairment

It is contraindicated in patients with moderate to severe renal

impairment (eGFR less than 30mL/min/1.73m²). The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. Empagliflozin may be used in patients with an eGFR greater than or equal to 45 mL/min/1.73m². 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

negatic impairment it should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Empagilliozin may be used in patients with 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

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.

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-M 5mg/500mg Tablets: Alu. Alu. Blister Pack of 2 x 7's. $\textbf{Diajard-M 12.5mg/500mg Tablets:} \ Alu. \ Alu. \ Blister \ Pack \ of \ 2 \times 7 's.$ Diajard-M 5mg/1000mg Tablets: Alu. Alu. Blister Pack of 2 x 7's. Diajard-M 12.5mg/1000mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.

ايم پا گليفاوزن + ميٺ فارن بائيڈروکلورائيڈ)

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعال کی جائے۔ بچوں کی پہنچ سے دور رکھیں۔ C °30 سے زیادہ درجہ حرارت پر نہر کھیں۔ خشک جگہ پر رکھیں۔ روشیٰ سے بحائیں۔

Manufactured by HIGHNOON LABORATORIES LTD 17.5 KM, Multan Road, Lahore, Pakistan.