Front

JARDY-MET XR™

(Empagliflozin + Metformin HCl Extended Release) Tablet

جارڈی-میٹ ایکس آر

COMPOSITION:

JARDY-MET XR 5/1000 Tablet:
Each film coated tablet contains:
Empagliflozin ..... 5 mg.
Metformin HCl (extended release) ..... 1000 mg.

Product Specs.: Innovator

JARDY-MET XR 10/1000 Tablet:
Each film coated tablet contains:
Empagliflozin ..... 10 mg.
Metformin HCl (extended release) ..... 1000 mg.

Product Specs.: Innovator

JARDY-MET XR 12.5/1000 Tablet:
Each film coated tablet contains:
Empagliflozin ..... 12.5 mg.
Metformin HCl (extended release) ..... 1000 mg.

Product Specs.: Innovator

JARDY-MET XR 25/1000 Tablet:
Each film coated tablet contains:
Empagliflozin ..... 25 mg.
Metformin HCl (extended release) ..... 1000 mg.

Product Specs.: Innovator

DESCRIPTION:

JARDY-MET XR tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: Empagliflozin and Metformin Hydrochloride.

Empagliflozin:

Empagliflozin is an orally-active inhibitor of the sodium glucose co-transporter 2 (SGLT2). The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3furanyl] oxy] phenyl] methyl] phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene. Metformin hydrochloride: Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C4H_{11}N_5.HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68

CLINICAL PHARMACOLOGY:

Mechanism of action:

JARDY-MET XR combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes:
Empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a member of the biguanide class. Empagliflozin Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

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

Pharmacodynamics:

Urinary glucose excretion: In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Urinary Volume: In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac electrophysiology: In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Pharmacokinetics:

Absorption: The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material.

Elimination: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. 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.

Metformin Hydrochloride:

Absorption: The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution: The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

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

SPECIAL POPULATIONS:

Geriatric:

Renal impairment: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in renally impaired patients have not been performed. Since metformin is contraindicated in patients with renal impairment, use of JARDY-MET is also contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR. Metformin hydrochloride: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic insufficiency: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in hepatically impaired patients have not been performed. However, use of metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use is not recommended in patients with hepatic impairment.

Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Body Mass Index, Gender, and Race:

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females. No studies of metformin pharmacokinetic parameters according to race have been performed.

Geriatrics: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in geriatric patients have not been performed.

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis.

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

Pediatric studies: Studies in pediatric patients have not been performed.

DRUG INTERACTIONS:

Pharmacokinetic drug interaction studies have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT_1A_1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT_1A_1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

INDICATION & USAGE:

JARDY-MET XR is a combination of empagliflozin and metformin HCl indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin.
JARDY-MET XR is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION:

In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating JARDY-MET XR.

Individualize the starting dose based on the patient's current regimen:

- In patients on metformin hydrochloride, switch to JARDY-MET XR containing a similar total daily dose of metformin hydrochloride and a total daily dose of empagliflozin 10 mg;
- In patients on empagliflozin, switch to JARDY-MET XR 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 JARDY-MET XR containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg
- The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride
- Take JARDY-MET XR orally once daily with a meal in the morning
  - Swallow tablets whole. Do not split, crush, dissolve, or chew before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin hydrochloride extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control
- JARDY-MET XR 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily
- JARDY-MET XR 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily

Recommended dosage in patients with renal impairment:

- Assess renal function prior to initiation and periodically, thereafter.
- JARDY-MET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

Discontinuation for iodinated contrast imaging procedures:

- Discontinue JARDY-MET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; 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:

JARDY-MET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR is less than 45 mL/min/1.73 m^2), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; end stage renal disease (ESRD) or patients on dialysis
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- Diabetic ketoacidosis should be treated with insulin [see Warnings and Precautions]
- History of serious hypersensitivity reaction to empagliflozin or metformin hydrochloride

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WARNINGS & PRECAUTIONS:

Lactic Acidosis: Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal cases/1000 patient-years). Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism.

Hypotension: Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin 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 if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. JARDY-MET XR is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with JARDY-MET XR 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 may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDY-MET XR should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. In many of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Acute kidney injury & impairment in renal function: Empagliflozin causes intravascular volume contraction and can cause renal impairment. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue SYNJARDY XR promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDY-MET XR. Renal function should be evaluated prior to initiation and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73m^2. Use of SYNJARDY XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

Radiological studies and surgical procedures: Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, SYNJARDY should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been confirmed to be normal.

Urosepsis and pyelonephritis: There have been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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: Empagliflozin 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. Metformin hydrochloride Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, 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 SUs and insulin) or ethanol.

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 mycotic genital infections. Monitor and treat as appropriate.

Urinary tract infections: Empagliflozin increases the risk for urinary tract infections. Monitor and treat as appropriate.

Vitamin B_{12} Levels: In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving JARDY-MET.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients JARDY-MET therapy, the drug should be promptly discontinued.

Increased low-Density lipoprotein cholesterol (LDL-C):
Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction or any other antidiabetic drug.

DRUG INTERACTIONS WITH METFORMIN HYDROCHLORIDE:

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic anhydrase inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JARDY-MET, as the risk of lactic acidosis may increase.

Drugs affecting glycemic control: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazine's, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving JARDY-MET, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATION:

Pregnancy: Based on animal data showing adverse renal effects, JARDY-MET XR is not recommended during the second and third trimesters of pregnancy. Limited available data in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

CLINICAL CONSIDERATIONS:

Disease-associated maternal and/or embryo/fetal risk: 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, still birth, and macrosomia related morbidity.

Lactation: There is no information regarding the presence of JARDY-MET XR or empagliflozin 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 (see Data). However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Empagliflozin is present in the milk of lactating rats (see Data). 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 a breastfed infant, advise women that use is not recommended while breastfeeding.

Pediatric use: The safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric use: Because 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.

Renal impairment: JARDY-MET XR is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).

ADVERSE REACTIONS:

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The following important adverse reactions are described below and elsewhere in the labeling:

- Lactic Acidosis
- Hypotension / Volume depletion
- Increased urination / Impairment in Renal Function
- Impaired Hepatic functions
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogueous
- Genital Mycotic Infections
- Urinary Tract Infections
- Vitamin B_{12} Deficiency
- Increased Low-Density Lipoprotein Cholesterol (LDL-C)

OVER DOSAGE:

In the event of an overdose contact the Hospital immediately. 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. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom over dosage is suspected.

INSTRUCTIONS:

Store below 30ºC. Protect from heat, sunlight & moisture. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

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JARDY-MET XR 12.5/1000 Tablet	:	Pack of 2 x 7 tablets.
JARDY-MET XR 25/1000 Tablet	:	Pack of 2 x 7 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

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25194-0013-002-0000-0000

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

Pharmacodynamics:

Urinary glucose excretion: In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Urinary Volume: In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac electrophysiology: In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Pharmacokinetics:

Absorption: The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material.

Elimination: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. 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.

Metformin Hydrochloride:

Absorption: The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution: The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

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

SPECIAL POPULATIONS:

Geriatric:

Renal impairment: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in renally impaired patients have not been performed. Since metformin is contraindicated in patients with renal impairment, use of JARDY-MET is also contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for

males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).
Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR. Metformin hydrochloride: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.
Hepatic insufficiency: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in hepatically impaired patients have not been performed. However, use of metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use is not recommended in patients with hepatic impairment.
Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.
Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.
Effects of Age, Body Mass Index, Gender, and Race:
Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.
Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females. No studies of metformin pharmacokinetic parameters according to race have been performed.
Geriatrics: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration in geriatric patients have not been performed.
Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis.
Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.
Pediatric studies: Studies in pediatric patients have not been performed.

DRUG INTERACTIONS:
Pharmacokinetic drug interaction studies have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT_1A_1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT_1A_1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

INDICATION & USAGE:
JARDY-MET XR is a combination of empagliflozin and metformin HCl indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin.
JARDY-MET XR is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION:
In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating JARDY-MET XR.
Individualize the starting dose based on the patient's current regimen:
- In patients on metformin hydrochloride, switch to JARDY-MET XR containing a similar total daily dose of metformin hydrochloride and a total daily dose of empagliflozin 10 mg;
- In patients on empagliflozin, switch to JARDY-MET XR 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 JARDY-MET XR containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg
- The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride
- Take JARDY-MET XR orally once daily with a meal in the morning
    - Swallow tablets whole. Do not split, crush, dissolve, or chew before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin hydrochloride extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control
- JARDY-MET XR 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily
- JARDY-MET XR 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily

Recommended dosage in patients with renal impairment:
- Assess renal function prior to initiation and periodically, thereafter.
- JARDY-MET XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

Discontinuation for iodinated contrast imaging procedures:
- Discontinue JARDY-MET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; 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:
JARDY-MET XR is contraindicated in patients with:
- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR is less than 45 mL/min/1.73 m^2), which may also result from

conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; end stage renal disease (ESRD) or patients on dialysis
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- Diabetic ketoacidosis should be treated with insulin [see Warnings and Precautions]
- History of serious hypersensitivity reaction to empagliflozin or metformin hydrochloride

WARNINGS & PRECAUTIONS:

Lactic Acidosis: Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal cases/1000 patient-years). Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism.

Hypotension: Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin 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 if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. JARDY-MET XR is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with JARDY-MET XR 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 may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDY-MET XR should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. In many of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Acute kidney injury & impairment in renal function: Empagliflozin causes intravascular volume contraction and can cause renal impairment. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age. Before initiating consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue SYNJARDY XR promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDY-MET XR. Renal function should be evaluated prior to initiation and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73m^2. Use of SYNJARDY XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

Radiological studies and surgical procedures: Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, SYNJARDY should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been confirmed to be normal.

Urosepsis and pyelonephritis: There have been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization 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: Empagliflozin 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. Metformin hydrochloride Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, 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 SUs and insulin) or ethanol.

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 mycotic genital infections. Monitor and treat as appropriate.

Urinary tract infections: Empagliflozin increases the risk for urinary tract infections. Monitor and treat as appropriate.

Vitamin B_{12} Levels: In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials.

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving JARDY-MET.

Hypoxic states: Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients JARDY-MET therapy, the drug should be promptly discontinued.

Increased low-Density lipoprotein cholesterol (LDL-C):
Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction or any other antidiabetic drug.

DRUG INTERACTIONS WITH METFORMIN HYDROCHLORIDE:

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Carbonic anhydrase inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JARDY-MET, as the risk of lactic acidosis may increase.

Drugs affecting glycemic control: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazine's, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving JARDY-MET, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATION:

Pregnancy: Based on animal data showing adverse renal effects, JARDY-MET XR is not recommended during the second and third trimesters of pregnancy. Limited available data in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

CLINICAL CONSIDERATIONS:

Disease-associated maternal and/or embryo/fetal risk: 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, still birth, and macrosomia related morbidity.

Lactation: There is no information regarding the presence of JARDY-MET XR or empagliflozin 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 (see Data). However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Empagliflozin is present in the milk of lactating rats (see Data). 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 a breastfed infant, advise women that use is not recommended while breastfeeding.

Pediatric use: The safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric use: Because 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.

Renal impairment: JARDY-MET XR is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).

ADVERSE REACTIONS:

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The following important adverse reactions are described below and elsewhere in the labeling:
- Lactic Acidosis

- Hypotension / Volume depletion
- Increased urination / Impairment in Renal Function
- Impaired Hepatic functions
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogueous
- Genital Mycotic Infections
- Urinary Tract Infections
- Vitamin B_{12} Deficiency
- Increased Low-Density Lipoprotein Cholesterol (LDL-C)

OVER DOSAGE:
In the event of an overdose contact the Hospital immediately. 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. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom over dosage is suspected.

INSTRUCTIONS:
Store below 30°C. Protect from heat, sunlight & moisture. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

JARDY-MET XR 5/1000 Tablet	:	Pack of 2 x 7 tablets.
JARDY-MET XR 10/1000 Tablet	:	Pack of 2 x 7 tablets.
JARDY-MET XR 12.5/1000 Tablet	:	Pack of 2 x 7 tablets.
JARDY-MET XR 25/1000 Tablet	:	Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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