Emglif-M™ XR

ایمگلِف-ایم ایکس آر
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(Empagliflozin / Metformin HCl)

12.5mg/1000mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Emglif-M XR Tablets 12.5mg/1000mg

Each film-coated tablet contains:
Empagliflozin................12.5mg
as Immediate Release Coating)
Metformin HCl U.S.P. ...1000mg
(as Extended Release Core)
Innovator's Specs.

DESCRIPTION

Emglif-M XR tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and Metformin HCl.

WARNING: LACTIC ACIDOSIS

•Post marketing cases of Metformin HCl-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of Metformin HCl-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin HCl-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and Metformin HCl plasma levels generally >5 mcg/mL.
•Risk factors for Metformin HCl-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
•If Metformin HCl-associated lactic acidosis is suspected, immediately discontinue Empagliflozin / Metformin HCl.

CLINICAL PHARMACOLOGY

Mechanism of Action: Empagliflozin/Metformin HCl XR tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and Metformin HCl. Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2) and Metformin HCl, 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. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. **Metformin HCl:** Metformin HCl is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. **PHARMACODYNAMICS: Empagliflozin:** 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: At a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin and placebo, there was no increase in QTc with either 25 mg or 200 mg empagliflozin. **PHARMACOKINETICS: Absorption:** Empagliflozin: Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. Metformin HCl: The absolute bioavailability of a Metformin HCl 500-mg tablet given under fasting conditions is approximately 50% to 60%. Food decreases the extent of and slightly delays the absorption of Metformin HCl, as shown by approximately a 40% lower Cmax, a 25% lower AUC, and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of Metformin HCl with food, compared to the same tablet strength administered fasting. **DISTRIBUTION: Empagliflozin:** The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Metformin HCl: The apparent volume of distribution (V/F) of Metformin HCl following single oral doses of immediate-release Metformin HCl tablets 850 mg averaged 654±358 L. Metformin HCl is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. **METABOLISM: Empagliflozin:** In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. **Metformin HCl:** Metformin HCl is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. **ELIMINATION: Empagliflozin:** 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. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. **Metformin HCl:** Renal clearance is approximately 3.5 times greater than creatinine clearance. 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.

INDICATIONS

Empagliflozin/Metformin HCl 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 when treatment with both empagliflozin and Metformin HCl is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of Empagliflozin/Metformin HCl on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established. Limitations of Use: Empagliflozn / Metformin HCl is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis

CONTRAINDICATIONS

Empagliflozn / Metformin HCl is contraindicated in patients with:
-Moderate to severe renal impairment (eGFR less than 45 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 HCl or any of the excipients in Empagliflozin/Metformin HCl.
-Diabetic pre-coma
-Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
-Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
-Hepatic impairment, acute alcohol intoxication, alcoholism

INTERACTIONS

Drug Interactions with Empagliflozin: Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. **Insulin or Insulin Secretagogues:** Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia. **Positive Urine Glucose Test:** 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. Interference with 1,5-anhydroglucitol (1,5-AG): Assay 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.
DRUG INTERACTIONS WITH METFORMIN HCl: Drugs that Reduce Metformin HCl Clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of Metformin HCl (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to Metformin HCl and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. **Carbonic Anhydrase Inhibitors:** Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and inducenon-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Empagliflozin/Metformin HCl may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients. **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, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetic, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Empagliflozin/Metformin HCl, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin/Metformin HCl, the patient should be observed closely for hypoglycemia. **Alcohol:** Alcohol is known to potentiate the effect of Metformin HCl on lactate metabolism. Warn patients against excessive alcohol intake while receiving Empagliflozin/Metformin HCl.

USE IN SPECIFIC POPULATION

Pregnancy: Empagliflozin / Metformin HCl is not recommended during the second and third trimesters of pregnancy. **Lactation:** The use of Empagliflozin / Metformin HCl is not recommended while breastfeeding. **Pediatric use:** Safety and effectiveness of Empagliflozin/Metformin HCl in pediatric patients under 18 years of age have not been established. **Geriatric use:** Initiation of therapy in this population is not recommended. **Hepatic patients:** Empagliflozin/Metformin HCl is not recommended in patients with hepatic impairment. **Renal Patients:** Empagliflozin/Metformin HCl is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m2)

PRECAUTIONS

Lactic acidosis: If Metformin HCl-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Empagliflozin/Metformin HCl. In Empagliflozin/Metformin HCl treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated Metformin HCl. **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. **Ketoacidosis:** If ketoacidosis is suspected, Empagliflozin/Metformin HCl should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. **Acute Kidney Injury and Impairment in Renal Function:** Renal function should be evaluated prior to initiation of Empagliflozin/Metformin HCl and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60mL/min/1.73m2. Use of Empagliflozin/Metformin HCl is contraindicated in patients with an eGFR less than 45mL/min/1.73 m2. **Urosepsis and Pyelonephritis:** 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. Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Patients treated with Empagliflozin/Metformin HCl 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 Empagliflozin/Metformin HCl, 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. **Vitamin B12 Levels:** 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. **Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate. **Administration of iodinated contrast agent:** Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in Metformin HCl accumulation and an increased risk of lactic acidosis. Metformin HCl should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable. **Cardiac function:** In patients with stable chronic heart failure, Empagliflozin/Metformin HCl may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, Empagliflozin/Metformin HCl is contraindicated due to the Metformin HCl component. **Surgery:** Metformin HCl must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable. **Lower limb amputations:** An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care. **Elevated haematocrit:** Haematocrit increase was observed with empagliflozin treatment.

ADVERSE REACTIONS

Very common: Hypoglycaemia (when used with sulphonylurea or insulin), Gastrointestinal symptoms
Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, Urinary tract infection (including pyelonephritis and urosepsis, thirst, Taste disturbance, Pruritus (generalised), Rash, Increased urination, Serum lipids increased. **Uncommon:** Diabetic ketoacidosis, Lactic acidosis, Vitamin B12 deficiency, Volume depletion, Liver function tests abnormalities, Hepatitis, Urticaria, Erythema, Angioedema, Dysuria, Blood creatinine increased/ Glomerular filtration rate decreased, Haematocrit increased

DOSAGE AND ADMINISTRATION

Recommended Dosing: In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating Empagliflozin/Metformin HCl
• Individualize the starting dose of Empagliflozin/Metformin HCl based on the patient's current regimen:
For Empagliflozin/Metformin HCl XR tablets: **By mouth: Adult 18-84 years:** 5mg/850mg - 5mg/1000mg twice daily, based on patient's current Metformin HCl dose, increased if necessary to 12.5mg/850mg - 12.5mg/1000mg twice daily.
Adult 85 years and over: Initiation not recommended.
For Empagliflozin/Metformin HCl XR tablets:
– In patients on Metformin HCl, switch to Empagliflozin/Metformin HCl containing a similar total daily dose of Metformin HCl and a total daily dose of empagliflozin 10 mg;
– In patients on empagliflozin, switch to Empagliflozin/Metformin HCl containing the same total daily dose of empagliflozin and a total daily dose of Metformin HCl extended-release 1000mg.
– In patients already treated with empagliflozin and Metformin HCl, switch to Empagliflozin/Metformin HCl containing the same total daily doses of empagliflozin and a similar total daily dose of Metformin HCl.
• Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of Metformin HCl 2000 mg and empagliflozin 25mg.
• The dose of Metformin HCl should be gradually escalated to reduce the gastrointestinal side effects due to Metformin HCl.
•Take Empagliflozin/Metformin HCl orally once daily with a meal in the morning. •Swallow Empagliflozin/Metformin HCl XR 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 HCl extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control. •Empagliflozin/Metformin HCl 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily. Empagliflozin/Metformin HCl 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 of Empagliflozin/Metformin HCl and periodically, thereafter. Empagliflozin/Metformin HCl is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m2. Discontinuation for Iodinated Contrast Imaging Procedures: Discontinue Empagliflozin/Metformin HCl 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 m2; 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 Empagliflozin/Metformin HCl if renal function is stable. **Overdosage:** 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 HCl is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated Metformin HCl from patients in whom Empagliflozin/Metformin HCl overdosage is suspected. **Metformin HCl:** Overdose of Metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin HCl has been established. Lactic acidosis has been reported in approximately 32% of Metformin HCl overdose cases.

INSTRUCTIONS Dosage as directed by the physician. Tablets must not be split, crushed, dissolved or chewed before swallowing. Store at 25°C, excursions permitted to 15°C-30°C. Protect from sunlight and moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

Emglif-M XR (Empagliflozin / Metformin HCl) tablets 12.5mg/1000mg are available in 2x7's Alu-Alu blister pack with leaflet.

ایمگلِف-ایم ایکس آر
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علامات / طریقہ استعمال :
ایمگلِف-ایم ایکس آر ٹیبلٹس ٹائپ 2 ذیابیطس کے ان مریضوں کے علاج کے لئے تجویز کردہ ہے جو دل کے امراض میں مبتلا ہوں۔

احتیاطی تدابیر:
ایمگلِف-ایم ایکس آر ٹیبلٹس کا استعمال دودھ پلانے والی ماؤں اور حمل کے دوسرے اور تیسرے ٹرائمیسٹر میں ممنوع ہے۔ بوڑھوں، جگر اور گردوں کے مریضوں میں ایمگلف-ایم کا استعمال ممنوع ہے۔ ۱۸ سال سے کم عمر کے بچوں میں دوا کا استعمال صرف ڈاکٹر کے مشورے سے کریں۔

مضر اثرات :
خون میں شوگر کی کمی، پیاس لگنا، خارش ہونا، بار بار پیشاب آنا، کیٹوایسیڈوسز، جینیٹل انفیکشنز، جگر کی خرابی گردوں کی خرابی اور بلڈ پریشر کا کم ہونا۔

ہدایات : خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ٹیبلٹس کو توڑنے، پیسنے، تحلیل کرنے اور چبانے سے گریز کریں۔
۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
سورج کی روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

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