Glempa-MXR Tablets

(Empagliflozin+Metformin HCl USP)

گلیمپا-ایم ایکس آر ٹیبلیٹس

(ایمپاگلائی فلوزن + میٹفارمن ہائیڈروکلورائیڈ)

WARNING: LACTIC ACIDOSIS

- Postmarketing cases of Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of Metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and Metformin plasma levels generally >5mcg/ml. - Risk factors for Metformin-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. - Steps to reduce the risk of and manage Metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information. - If Metformin-associated lactic acidosis is suspected, immediately discontinue **Glempa-MXR** and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

COMPOSITION:

Glempa-MXR 5mg/1000mg Tablets
Each film coated tablet contains:
Empagliflozin (as Immediate Release Coating) 5mg
Metformin HCl USP (as Extended Release Core) ... 1000mg [Innovator's Specs.]

Glempa-MXR 10mg/1000mg Tablets
Each film coated tablet contains:
Empagliflozin (as Immediate Release Coating) 10mg
Metformin HCl USP (as Extended Release Core) ... 1000mg [Innovator's Specs.]

Glempa-MXR 12.5mg/1000mg Tablets
Each film coated tablet contains:
Empagliflozin (as Immediate Release Coating) 12.5mg
Metformin HCl USP (as Extended Release Core) ..... 1000mg [Innovator's Specs.]

Glempa-MXR 25mg/1000mg Tablets
Each film coated tablet contains:
Empagliflozin (as Immediate Release Coating) 25mg
Metformin HCl USP (as Extended Release Core) ... 1000mg [Innovator's Specs.]

DESCRIPTION: Empagliflozin: Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2).
Metformin hydrochloride: Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide.

INDICATIONS: Glempa-MXR is a combination of Empagliflozin and Metformin hydrochloride indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
Limitation of Use: Glempa-MXR is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

DOSAGE AND ADMINISTRATION: Prior to Initiation of Glempa-MXR: - Assess renal function before initiating **Glempa-MXR** and as clinically indicated. - In patients with volume depletion, correct this condition before initiating **Glempa-MXR**.
Recommended Dosage and Administration: Individualize the starting dose of **Glempa-MXR** based on the patient's current regimen: - In patients on metformin HCl, switch to **Glempa-MXR** containing a similar total daily dose of Metformin HCl and a total daily dose of Empagliflozin 10mg. - In patients on empagliflozin, switch to **Glempa-MXR** 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 **Glempa-MXR** containing the same total daily doses of Empagliflozin and a similar total daily dose of Metformin HCl. - Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of Empagliflozin 25mg and metformin HCl 2000mg. - The dose of Metformin HCl should be gradually escalated to reduce the gastrointestinal side effects due to Metformin. - Take **Glempa-MXR** orally once daily with a meal in the morning. - Swallow **Glempa-MXR** tablets whole. Do not split, crush, dissolve, or chew. - **Glempa-MXR** 10mg/1000mg and 25mg/1000 mg tablets should be taken as a single tablet once daily. **Glempa-MXR** 5mg/1000mg and 12.5mg/1000mg tablets should be taken as two tablets together once daily.
Dosage Recommendations in Patients with Renal Impairment: - Initiation of **Glempa-MXR** is not recommended in patients with an eGFR less than 45ml/min/1.73m^2, due to the Metformin component. - **Glempa-MXR** is contraindicated in patients with an eGFR less than 30ml/min/1.73m^2 or in patients on dialysis.
Discontinuation for Iodinated Contrast Imaging Procedures: Discontinue **Glempa-MXR** at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60ml/min/1.73m^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 **Glempa-MXR** if renal function is stable.

CLINICAL PHARMACOLOGY: 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. 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 is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose.
Pharmacokinetics: Administration of Empagliflozin and Metformin HCl Tablets with food resulted in no change in overall exposure of Empagliflozin. For Metformin hydrochloride extended-release

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high-fat meals increased systemic exposure to Metformin (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while C_{max} is not affected. Meals prolonged T_{max} by approximately 3 hours.
Empagliflozin: Absorption: 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 1870nmol·h/L and 259nmol/L, respectively, with 10mg Empagliflozin once daily treatment, and 4740nmol·h/L and 687nmol/L, respectively, with 25mg empagliflozin once daily treatment.
Distribution: The apparent steady-state volume of distribution was estimated to be 73.8L based on a population pharmacokinetic analysis.
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.
Metformin hydrochloride: Absorption: Following a single oral dose of 1000mg (2 x 500mg tablets) metformin hydrochloride extended-release after a meal, the time to reach maximum plasma Metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours.
Distribution: The apparent volume of distribution of Metformin following single oral doses of immediate-release Metformin hydrochloride tablets 850mg averaged 654±358L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.
Metabolism: Intravenous single-dose studies in normal subjects demonstrate that Metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.
Elimination: Metformin has 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.

CONTRAINDICATIONS: Empagliflozin and Metformin HCl Tablets are contraindicated in patients with: ▪ Severe renal impairment (eGFR less than 30ml/min/1.73m^2), end stage renal disease, or dialysis. ▪ Acute or chronic metabolic acidosis, including diabetic ketoacidosis. ▪ Hypersensitivity to Empagliflozin, Metformin or any of the excipients in Empagliflozin and Metformin HCl Tablets, reactions such as angioedema have occurred.

WARNINGS AND PRECAUTIONS:
Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue Empagliflozin and Metformin HCl Tablets, evaluate and treat promptly. Before initiating Empagliflozin and Metformin HCl Tablets, consider risk factors for ketoacidosis. Patients on Empagliflozin and Metformin HCl Tablets may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.
Volume Depletion: Before initiating Empagliflozin and Metformin HCl Tablets, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy.
Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.
Hypoglycemia: Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating Empagliflozin and Metformin HCl Tablets.
Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.
Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., angioedema) have occurred with Empagliflozin. If hypersensitivity reactions occur, discontinue Empagliflozin and Metformin HCl Tablets, treat promptly, and monitor until signs and symptoms resolve.
Vitamin B_{12} Deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.

SIDE EFFECTS: The following are the side effects as described below:
▪ low blood sugar ▪ gas ▪ urinary tract infection ▪ stomach discomfort ▪ stuffy or runny nose and sore throat ▪ indigestion ▪ yeast infections in females ▪ weakness ▪ diarrhea ▪ headache ▪ nausea or vomiting.

DRUG INTERACTIONS: ▪ Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. ▪ Drugs that reduce Metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of Metformin. Consider the benefits and risks of concomitant use. ▪ Alcohol can potentiate the effect of Metformin on lactate metabolism. Warn patients against excessive alcohol intake.

OVERDOSE: Overdose of Metformin HCl has occurred, including ingestion of amounts greater than 50g. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases. Metformin is dialyzable with a clearance of up to 170ml/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin overdosage is suspected.

INSTRUCTIONS: Store below 30° C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION:
Glempa-MXR 5mg/1000mg Tablets are available in pack sizes of 14's.
Glempa-MXR 10mg/1000mg Tablets are available in pack sizes of 14's.
Glempa-MXR 12.5mg/1000mg Tablets are available in pack sizes of 14's.
Glempa-MXR 25mg/1000mg Tablets are available in pack sizes of 14's.

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دُور رکھیں۔

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