Glempa-M Tablets

گلیمپا-ایم ٹیبلیٹس

(Empagliflozin+Metformin HCl USP)

(ایمپاگلائی فلوزن + میٹفارمن ہائیڈروکلورائیڈ یو ایس پی)

WARNING: LACTIC ACIDOSIS

Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, discontinue **Glempa-M** Tablets and hospitalize the patient immediately.

COMPOSITION:

Glempa-M 5mg / 500mg tablet: Each film coated tablet contains:
Empagliflozin 5mg
Metformin Hydrochloride USP ... 500mg [Innovator's Specs.]

Glempa-M 5mg / 850mg tablet: Each film coated tablet contains:
Empagliflozin 5mg
Metformin Hydrochloride USP ... 850mg [Innovator's Specs.]

Glempa-M 5mg / 1000mg tablet: Each film coated tablet contains:
Empagliflozin 5mg
Metformin Hydrochloride USP ... 1000mg [Innovator's Specs.]

Glempa-M 12.5mg / 500mg tablet: Each film coated tablet contains:
Empagliflozin 12.5mg
Metformin Hydrochloride USP ... 500mg [Innovator's Specs.]

Glempa-M 12.5mg / 850mg tablet: Each film coated tablet contains:
Empagliflozin 12.5mg
Metformin Hydrochloride USP ... 850mg [Innovator's Specs.]

Glempa-M 12.5mg / 1000mg tablet: Each film-coated tablet contains:
Empagliflozin 12.5mg
Metformin Hydrochloride USP ... 1000mg [Innovator's Specs.]

DESCRIPTION: Glempa-M contains two oral anti-hyperglycemic 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). Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

INDICATIONS: Glempa-M (Empagliflozin+Metformin HCl) is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise: - In patients insufficiently controlled on their maximally tolerated dose of Metformin HCl alone. - In combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with Metformin HCl and these medicinal products. - In patients already being treated with the combination of Empagliflozin and Metformin HCl as separate tablets.

DOSAGE AND ADMINISTRATION: Recommended Dosing: The recommended dose of **Glempa-M** (Empagliflozin+Metformin HCl) is one tablet twice daily. The dosage should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 10mg or 25mg of Empagliflozin, while not exceeding the maximum recommended daily dose of 2000mg of Metformin HCl. **Glempa-M** (Empagliflozin+Metformin HCl) should be given with meals to reduce the gastrointestinal side effects due to Metformin.
Special populations: Patients with renal impairment: No dose adjustment is recommended for patients with mild renal impairment. **Glempa-M** (Empagliflozin+Metformin HCl) is contraindicated for use in patients with moderate or severe renal impairment (creatinine clearance <60ml/min). Renal function should be assessed before initiation of treatment with Metformin HCl containing products and at least annually there after. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
Patients with Hepatic impairment: Glempa-M (Empagliflozin+Metformin HCl) must not be used in patients with hepatic impairment.
Elderly: Glempa-M (Empagliflozin+Metformin HCl) should be used with caution in elderly patients. Monitoring of renal function is necessary to aid in prevention of Metformin-associated lactic acidosis, particularly in elderly patients. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Due to the limited therapeutic experience with Empagliflozin in patients aged 85 years and older, initiation of therapy is not recommended.

CLINICAL PHARMACOLOGY: Mechanism of Action: Empagliflozin: 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 stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin HCl may active via three mechanisms; - By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis. - In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization. - By delaying intestinal glucose absorption.

PHARMACOKINETICS: Absorption: Empagliflozin: After oral administration, Empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5h post-dose. The steady state mean plasma AUC and C_{max} were 1870nmol.h and 259nmol/L with Empagliflozin 10mg and 4740nmol.h and 687nmol/L with Empagliflozin 25mg once daily treatment.
Metformin HCl: After an oral dose of Metformin HCl, T_{max} is reached in 2.5 hours. The absolute bioavailability of a single dose 500mg dose is reported to be about 50% to 60% given under fasting condition. Food decreases the extent and slightly delays the absorption of Metformin HCl.
Distribution: Empagliflozin: The apparent steady-state volume of distribution was estimated to be 73.8L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

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Metformin HCl: Metformin HCl is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound at usual clinical doses and dosing schedules of Metformin HCl tablets, steady-state plasma concentrations of Metformin HCl are reached within 24-48 hours and are generally < 1mcg/ml.
Metabolism: Empagliflozin: Systemic exposure of each metabolite was less than 10% of total drug-related material. The primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphospho glucuronosyltransferases, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.
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 hours and apparent oral clearance was 10.6 L/h. Following administration of an oral [^{14}C]-Empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in feces (41.2%) or urine (54.4%). 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 HCl: 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.

CONTRAINDICATIONS: The combination of Empagliflozin+Metformin HCl is contraindicated in: - Patients with hypersensitivity to Empagliflozin, Metformin HCl or to any excipient of the product. - Moderate to severe renal impairment, end stage renal disease, or dialysis. - Acute or chronic metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic ketoacidosis should be treated with insulin. - Diabetic pre-coma. - Acute conditions with the potential to alter renal function such as dehydration,severe infection, shock. - Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock, pulmonary embolism, acute significant blood loss, sepsis, gangrene, pancreatitis. - During or immediately following surgery where insulin is essential, elective major surgery. - Hepatic impairment, acute alcohol intoxication, alcoholism (due to the metformin component). - Lactation.

WARNINGS AND PRECAUTIONS: - Genital Mycotic Infections - Hypersensitivity Reactions - Increased Low-Density Lipoprotein Cholesterol (LDL-C) - Urine laboratory assessments - Effects on ability to drive and use machines - Elevated hematocrit - Lactic Acidosis - Diabetic ketoacidosis - Acute Kidney Injury and Impairment in Renal Function - Urosepsis and Pyelonephritis - Cardiac function - Surgery - Risk for volume depletion - Elderly

PREGNANCY AND LACTATION: Pregnancy: When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with Empagliflozin+Metformin HCl, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus associated with abnormal blood glucose levels.
Nursing Mothers: Metformin HCl is excreted into human breast milk. It is unknown whether Empagliflozin is excreted in human milk. Empagliflozin+Metformin HCl should not be administered during nursing.

SIDE EFFECTS: **Very Common:** Hypoglycemia (when used with sulphonylurea or insulin) and gastrointestinal symptoms.
Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection (including pyelonephritis and urosepsis), thirst, taste disturbance, pruritus (generalized), rash, increased urination and increased serum lipids.
Uncommon: Volume depletion, urticaria, dysuria, blood creatinine increased/glomerular filtration rate decreased and hematocrit increased.
Rare: Diabetic ketoacidosis.
Very Rare: Lactic acidosis, Vitamin B_{12} deficiency, liver function tests abnormalities,hepatitis and erythema.
Not known: Necrotizing Fasciitis of the perineum (Fournier's gangrene) and Angioedema.

OVERDOSAGE: Empagliflozin: Single doses of up to 800mg Empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy subjects and multiple daily doses of up to 100mg Empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume.
Treatment: In the event of an overdose with Empagliflozin, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute supportive treatment) as dictated by the patient's clinical status.
Metformin HCl: In case of Metformin HCl overdose (greater than 50g), 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.

DRUG INTERACTIONS: Empagliflozin: Diuretics: Co-administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
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.
Metformin HCl: - Drugs that Reduce Metformin Clearance. - Carbonic Anhydrase Inhibitors. - Drugs Affecting Glycemic Control. - Alcohol. - Cimetidine. - Anticoagulants. - Nifedipine. - Organic Cation Transporters (OCT). - Glucocorticoids. - Insulin or Insulin Secretagogues.

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

PRESENTATION: Glempa-M (5mg/500mg, 5mg/850mg, 5mg/1000mg, 12.5mg/500mg, 12.5mg/850mg, 12.5mg/1000mg) tablets are available in the Blister pack of 14's.

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

Manufactured by:
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