EMPANEXT-M Tablet

(Innovator's Specification)

Empagliflozin (Manufacturer Specification)

Metformin Hcl (USP Specifications)

COMPOSITION:

Each film coated tablet contains:

Empanext-M 5/500 Tablet:

Empagliflozin ..... 5 mg.
Metformin HCl ..... 500 mg.
(Innovators Specification)

Empanext-M 12.5/500 Tablet:

Empagliflozin ..... 12.5 mg.
Metformin HCl ..... 500 mg.
(Innovators Specification)

Empanext-M 5/1000 Tablet:

Empagliflozin ..... 5 mg
Metformin HCl ..... 1000 mg.
(Innovators Specification)

Empanext-M 12.5/1000 Tablet:

Empagliflozin ..... 12.5 mg.
Metformin HCl ..... 1000 mg.
(Innovators Specification)

DESCRIPTION:

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-3 furanyl] oxy] phenyl] methyl] phenyl]-, (1S). Its molecular formula is C23H27ClO7 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 C4H11N5.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:

Empanext-M 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

Empagliflozin:

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 Cmax 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%.

Metformin Hcl:

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 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 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 <1mcg/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.

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 UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Indication and usage

Empanext-M 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. Empanext-M is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION:

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

- In patients on metformin, switch to Empanext-M containing empagliflozin 5 mg with a similar total daily dose of metformin;
- In patients on empagliflozin, switch to Empanext-M containing metformin 500 mg with a similar total daily dose of empagliflozin;
- In patients already treated with empagliflozin and metformin, switch to Empanext-M containing the same total daily doses of each component.
- Take Empanext-M twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin
- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating Empanext-M.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and empagliflozin 25 mg.

Recommended Dosage in Patients with Renal Impairment:

- Assess renal function prior to initiation and periodically, thereafter
- Do not initiate or continue in patients with serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females.
- In patients eligible based on creatinine cut off criteria do not initiate or continue if eGFR is persistently less than 45 mL/min/1.73 m2.
- In patients eligible based on creatinine cut off criteria, no dose adjustment is needed if eGFR is greater than or equal to 45 mL/min/1.73 m2.

CONTRAINDICATIONS:

Empanext-M 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), 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.

Impairment in Renal Function: Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. Metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, 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 m2.

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, Empanext-M 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.

Impaired Hepatic Function: Because impaired hepatic function has been associated with some cases of lactic acidosis with metformin therapy, Empanext-M should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

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 B12 Levels: In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-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 Empanext-M. ***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 Empanext-M 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 Empanext-M 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 Empanext-M, the patient should be observed closely for hypoglycemia.

USE IN SPECIFIC POPULATION:

Use in Specific Populations:

Pregnancy: Category C

There are no adequate and well-controlled studies in pregnant women or its individual components. Empanext-M should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: No studies in lactating animals have been conducted with the combined components. In studies performed with the individual components, both empagliflozin and metformin were secreted in the milk of lactating rats. It is not known whether empagliflozin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants may exist from, a decision should be made whether to discontinue nursing or to discontinue Empanext-M, taking into account the importance of the drug to the mother.

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, monitor renal function more frequently after initiating Empanext-M in the elderly and then adjust dose based on renal function.

Renal Impairment: Empanext-M 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 m2).

Hepatic Impairment: Empanext-M should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

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 B12 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:

Empanext-M 5/500 Tablet:	Pack of 2 x 7 tablets
Empanext-M 12.5/500 Tablet:	Pack of 2 x 7 tablets
Empanext-M 5/1000 Tablet:	Pack of 2 x 7 tablets
Empanext-M 12.5/1000 Tablet:	Pack of 2 x 7 tablets

Lactose and Gluten Free

ایمپانیکسٹ-ایم
ٹیبلٹ

(ایمپاگلافلوزن + میٹفارمین ایچ سی ایل)

12.5 ملی گرام 500 ملی گرام

12.5 ملی گرام 1000 ملی گرام

5 ملی گرام 500 ملی گرام

5 ملی گرام 1000 ملی گرام

فلم کوٹڈ گولیاں

خوراک و ہدایات:

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخے کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر

روشنی، گرمی اور نمی سے محفوظ رکھیں۔

NEXT PHARMACEUTICAL

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