

EMPAFLIZIN-M (Empagliflozin and Metformin HCl) Tablets

4000002905

Innovator's Specifications

Empagliflozin-M 5mg/500mg Tablets: Each film coated tablet contains Empagliflozin USP 5 mg and Metformin hydrochloride USP 500 mg	5 mg
Empagliflozin-M 5mg/1000mg Tablets: Each film coated tablet contains Empagliflozin USP 5 mg and Metformin hydrochloride USP 1000 mg	5 mg
Empagliflozin-M 12.5mg/500mg Tablets: Each film coated tablet contains Empagliflozin USP 12.5 mg and Metformin hydrochloride USP 500 mg	12.5 mg
Empagliflozin-M 12.5mg/1000mg Tablets: Each film coated tablet contains Empagliflozin USP 12.5 mg and Metformin hydrochloride USP 1000 mg	12.5 mg

WARNING: LACTIC ACIDOSIS

- Post marketing 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 (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate:pyruvate ratio, and metformin plasma levels generally <5 mg/mL.
- Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonyl anhydrase inhibitors such as toipramate), 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-associated lactic acidosis is suspected, immediately discontinue Empagliflozin (Empagliflozin and Metformin HCl) and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION

Empagliflozin-M (Empagliflozin and Metformin HCl) 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 (1S)-1-(4-ethylpiperidin-1-yl)-1H-imidazo[5,1-b]pyridin-3-ylurea hydrochloride (1S)-1H-imidazo[5,1-b]pyridin-3-ylurea hydrochloride. Its molecular formula is C₂₃H₂₇FClO₂.

Metformin hydrochloride: Metformin is a biguanide with antihyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin hydrochloride has a molecular formula of C₄H₁₁N₅HCl and a molecular weight of 165.63.

CLINICAL PARTICULARS

Therapeutic Indications

- Empagliflozin (empagliflozin and metformin HCl) is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.
- Empagliflozin, when used as a component of Empagliflozin-M (empagliflozin and metformin hydrochloride), is indicated in patients with type 2 diabetes mellitus to reduce the risk of:
 - Cardiovascular death in adults with established cardiovascular disease.
 - Cardiovascular death and hospitalization for heart failure in adults with heart failure.

Contraindications

- Empagliflozin-M (Empagliflozin and Metformin HCl) is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketonacidosis. It may increase the risk of diabetic ketoacidosis in these patients.
- Because of the metformin component, Empagliflozin-M (empagliflozin and metformin hydrochloride) is not recommended for use in patients with heart failure without type 2 diabetes mellitus.

Posology and method of administration

Recommended Dosage in Adults

When switching to Empagliflozin-M (empagliflozin and metformin HCl combination) from:

- Metformin HCl initiate Empagliflozin-M (empagliflozin and metformin HCl combination) at a similar total daily dosage of metformin HCl and total empagliflozin dosage of 10 mg.
- Empagliflozin: initiate Empagliflozin-M (empagliflozin and metformin HCl combination) at the same total daily dosage of empagliflozin and a total daily metformin HCl dosage of 1,000 mg.
- Empagliflozin and metformin HCl: initiate Empagliflozin-M (empagliflozin and metformin HCl combination) at the same total daily dosages of each component.

Recommended dosage of Empagliflozin-M (empagliflozin and metformin HCl combination):

- The recommended total daily dosage of empagliflozin is 10 mg.
- Take Empagliflozin-M (Empagliflozin and Metformin HCl) 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 Empagliflozin-M (empagliflozin and metformin HCl combination).
- 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 Children (Aged 10 Years and Older)

- Individualize the dosage of Empagliflozin-M (empagliflozin and metformin hydrochloride) based on the patient's current regimen.
- Monitor effectiveness and tolerability, and adjust dosage as appropriate, not to exceed the maximum total daily dosage of empagliflozin 25 mg and metformin HCl 2,000 mg.
- Take Empagliflozin-M (empagliflozin and metformin hydrochloride) orally twice daily with meals; with gradual dose escalation to reduce gastrointestinal adverse reactions with metformin.

Recommended Dosage in Pediatric Patients with Renal Impairment

- Contraindicated in patients with an eGFR less than 30 mL/(min^{1.73} m²) or in patients on dialysis.
- Initiation of Empagliflozin-M (empagliflozin and metformin hydrochloride) is not recommended in patients with an eGFR less than 45 mL/(min^{1.73} m²) on dialysis.
- Recommendations Regarding Missed Dose

• If a dose is missed, instruct patients to take the dose as soon as possible.

• Do not double up the next dose.

Method of Administration

Empagliflozin-M (Empagliflozin and Metformin HCl) should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. All patients should continue their diet with an adequate distribution of carbohydrates intake during the day. Overweight patients should continue their energy restricted diet.

CONTRAINDICATION

- Empagliflozin and Metformin HCl combination is contraindicated in patients with:
 - Severe renal impairment (eGFR less than 30 mL/(min^{1.73} m²), end stage renal disease, or dialysis.
 - Acute or chronic metabolic acidosis, including diabetic ketoacidosis and lactic acidosis.
 - History of serious hypersensitivity reaction to empagliflozin or metformin hydrochloride or to any of the excipients.
 - Hepatic pre-eclampsia.
 - 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: compensated heart failure, respiratory failure, recent myocardial infarction, shock.
 - Hepatic impairment, acute alcohol intoxication, alcoholism

WARNINGS AND PRECAUTIONS

Lactic Acidosis: Lactic acidosis is a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhea) or vomiting, fever or reduced fluid intake, metformin should be temporarily discontinued and contact with a health care professional is recommended. Patients and/or care-givers should be informed of the risk of lactic acidosis.

In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.

Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate:pyruvate ratio.

Ketoadcidosis: Reports of ketoadcidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and post marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Patients treated with empagliflozin and metformin hydrochloride combination may present with signs and symptoms similar to those associated with severe metabolic acidosis. Such patients should be assessed for ketoadcidosis regardless of presenting blood glucose levels, as ketoadcidosis associated with empagliflozin and metformin hydrochloride combination may be present even if blood glucose levels are less than 250 mg/dL. If ketoadcidosis is suspected, empagliflozin and metformin hydrochloride combination should be discontinued and patient should be evaluated, and prompt treatment should be instituted. Before initiating empagliflozin and metformin hydrochloride combination, consider factors in the patient history that may predispose to ketoadcidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

Hypotension: Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment (eGFR less than 60 mL/(min^{1.73} m²)), the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating Empagliflozin and Metformin HCl combination, 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.

Empagliflozin in Renal Function

Empagliflozin increases serum creatinine and decreases eGFR. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, Empagliflozin and Metformin HCl combination is contraindicated in patients with an eGFR below 30 mL/(min^{1.73} m²).

Before initiation of therapy with Empagliflozin and Metformin HCl combination and at least annually thereafter, estimated glomerular filtration rate (eGFR) should be monitored. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and Empagliflozin and Metformin HCl combination discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution.

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis.

Discontinue empagliflozin and metformin combination at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 intravascular iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart empagliflozin and metformin HCl combination if renal function is stable.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a higher prevalence of hypoxic hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Surgery: Empagliflozin and Metformin HCl combination should be temporarily discontinued for any surgical procedure that involves procedures not associated with reduced intake of food and fluids and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

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

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. In adult patients, the mean plasma glucose levels were similar in patients receiving Empagliflozin HCl combination in use in combination with insulin secretagogues (e.g., sulfonylureas or insulin). In pediatric patients aged 10 years and older, the risk of hypoglycemia was higher with empagliflozin regardless of insulin use. The risk of hypoglycemia may be increased in patients with a history of use of sufficient doses of either oral or intravenous administered insulin secretagogues or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Genital and Urinary Tract Infections: Genital and urinary tract infections have been reported in patients with a history of chronic 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 UTI including urethritis and pyelonephritis. Monitor and treat as appropriate.

Vitamin B₁₂ Levels: In controlled clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approx. 7% of metformin-treated patients. The decrease in vitamin B₁₂ levels appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis and vitamin B₁₂ at 2 to 3 years intervals is advised in patients on Empagliflozin and Metformin HCl combination and any apparent abnormalities should be appropriately monitored and managed.

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 Empagliflozin and Metformin HCl combination.

Shock States: Cardiovascular collapse (shock) from whatever cause (e.g., acute CHF, acute MI, and other conditions characterized by hypoxemia) has been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Empagliflozin and Metformin HCl combination 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.

Diabetic Ketoacidosis: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Empagliflozin and Metformin HCl combination, or any other antidiabetic drug.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients treated with empagliflozin and metformin hydrochloride combination 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 and metformin hydrochloride combination, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Hypersensitivity Reactions: There have been post marketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue empagliflozin and Metformin combination, treat promptly per standard of care, and monitor until signs and symptoms resolve.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C. Based on animal data showing adverse renal effects from empagliflozin, Empagliflozin and metformin HCl combination are not recommended for use during the second and third trimesters of pregnancy. **Nursing Mothers:** There is limited information regarding the presence of empagliflozin or metformin 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 breast milk. The safety profile of lactating patients treated with empagliflozin is similar to that observed in adults with type 2 diabetes mellitus, with the exception of hypoglycemia risk which was higher in pediatric patients aged 10 years and older 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, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of Empagliflozin and metformin HCl combination is not recommended while breastfeeding.

Pediatric Use: The safety and effectiveness of empagliflozin and metformin hydrochloride combination as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. The safety profile of pediatric patients treated with empagliflozin and metformin HCl combination is similar to that observed in adults with type 2 diabetes mellitus, with the exception of hypoglycemia risk which was higher in pediatric patients aged 10 years and older 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, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of Empagliflozin and metformin HCl combination is not recommended while breastfeeding.

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Geriatric Usage: Assess renal function more frequently in empagliflozin and metformin HCl combination treated geriatric patients because there is a greater proportion of age-associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients. The recommended dosage for the metformin component of empagliflozin and metformin HCl combination in geriatric patients should usually start at a maximum of 750 mg twice daily.

Renal Impairment: Empagliflozin and metformin HCl combination should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m² due to the metformin component and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²) and stage renal disease, or dialysis.

Empagliflozin: The glucose lowering benefit of empagliflozin 25 mg decreased in adult patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with renal impairment. In the trial of pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, patients with an eGFR less than 60 mL/min/1.73 m² were not enrolled.

Metformin: Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

Hepatic Impairment: Use of metformin HCl in patients with hepatic impairment has been associated with some cases of lactic acidosis. Empagliflozin and metformin HCl combination is not recommended in patients with hepatic impairment.

DRUG INTERACTIONS

Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which may enhance the potential for volume depletion.

Oral or Insulin Secretagogues: Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

Glucose 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-DG AUC Assay: Monitoring glycemic control with 1,5-DG assay is not recommended as measurements of 1,5-DG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Cationic Drugs: Coadministration of these drugs and dose adjustment of Empagliflozin and Metformin HCl combination and/or interfering drug is recommended in patients who are taking cationic medications (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are excreted via the proximal renal tubular secretory system.

Cationic Anhydrase Inhibitors: Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Use these drugs with caution in patients treated with Empagliflozin and Metformin HCl combination, as the risk of lactic acidosis may increase.

Diuretics/Antacids/Calcium Channel Blockers: Certain drugs tend to produce hypocalcemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenolphthalein, nifedipine, sympathomimetics, calcium channel blocking drugs, and sodiumized. When such drugs are administered to a patient receiving Empagliflozin and Metformin HCl combination, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin and Metformin HCl combination, the patient should be observed closely for hypoglycemia.

Drugs that Reduce Metformin Clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 (OCT2) / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, duloxetine, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Alcohol: Alcohol may potentiate the potential of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving empagliflozin and metformin combination.

Lithium: Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during Empagliflozin and metformin combination initiation and dosage changes.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling: Lactic Acidosis, Ketoacidosis, Hypotension, Renal Function Impairment, Hepatic Impairment, Hypoglycemia, Volume Depletion, Interference with Insulin and Insulin Secretagogues, Genital Mycotic Infections, Urinary Tract Infections, Vitamin B12 Deficiency, Increased Low-Density Lipoprotein Cholesterol (LDL-C), Hypersensitivity reactions, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene).

Pediatric Patients: In clinical trials with metformin HCl immediate-release tablets in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.

OVERDOSAGE

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected. Removal of empagliflozin by hemodialysis has not been studied.

CLINICAL PHARMACOLOGY

Mechanism of Action

Empagliflozin and Metformin HCl combination Tablet combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin and metformin.

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 hydrochloride: Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

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 mgms per day with 10 mg empagliflozin and 78 mgms 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: After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

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).

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.

Pediatric Patients: The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

Metformin hydrochloride

Absorption: The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 20% lower AUC_{0-∞}, 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_D) 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.

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 50% 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.

Pediatric Patients: After administration of a single oral metformin HCl 500 mg immediate-release tablet with food, geometric mean metformin C_{max} and AUC_{0-∞} differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

Specific Populations

Racial Impairment: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administering empagliflozin and metformin HCl combination in renally impaired patients have not been performed. Empagliflozin: 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: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased.

Hepatic Impairment: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administering empagliflozin and metformin HCl combination in hepatically impaired patients have not been performed.

Empagliflozin: In adult patients 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 HCl: 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.

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

HOW SUPPLIED

Empagler-M 5mg/500mg Tablets Pack of 14 Tablets

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Empagler-M 12.5mg/500mg Tablets Pack of 14 Tablets

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STORAGE

Do not store above 30°C.

The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from moisture, heat, light and children.

To be dispensed on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:

FEROZSONS
LABORATORIES LIMITED

P. O. Ferozsons, Nowshera-Pakistan

Mfg. Lic. No. 000038