02-09-0375

Empagen-M XR

(Empagliflozin and Metformin HCl Extended-Release) Tablets

Innovator's Specifications

Empagen-M XR 5mg/1000mg Tablets: Each film coated tablet contains: Empagliflozin 5mg Metformin HCl USP 1000mg (as extended-release).

Empagen-M XR 10mg/1000mg Tablets: Each film coated tablet contains: Empagliflozin 10mg Metformin HCl USP 1000mg (as extended-release).

Empagen-M XR 12.5mg/1000mg Tablets: Each film coated tablet contains: Empagliflozin 12.5mg Metformin HCl USP 1000mg (as extended-release).

Empagen-M XR 25mg/1000mg Tablets: Each film coated tablet contains: Empagliflozin 25mg Metformin HCl USP 1000mg (as extended-release).

WARNING: LACTIC ACIDOSIS

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.
- Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.
- If lactic acidosis is suspected, discontinue Empagliflozin and Metformin HCl Extended-Release tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1 DESCRIPTION

Empagen-M XR tablets, for oral use, contain two antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and metformin hydrochloride.

1.1 **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 $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.

1.2 Metformin hydrochloride: Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. Metformin Hcl has a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63.

2 CLINICAL PARTICULARS

2.1 Therapeutic indications

Empagen-M XR 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 (CV) death in adults with type 2 diabetes mellitus and established cardiovascularCV disease**.** However, the effectiveness of empagliflozin and metformin HCl extended-release combination on reducing the risk of CV death in adults with type 2 diabetes mellitus and CV disease has not been established.

2.2 Limitations of Use

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

2.3 Posology and method of administration

2.3.1 Recommended Dosage

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating Empagen-M XR.
- Individualize the starting dose of Empagen-M XR based on the patient's current regimen:
  - In patients on metformin HCl, switch to Empagen-M XR containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg;
  - In patients on empagliflozin, switch to Empagen-M XR containing the same total daily dose of empagliflozin and a total daily dose of metformin HCl extended-release 1000 mg;
  - In patients already treated with empagliflozin and metformin HCl, switch to Empagen-M XR 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 25 mg.
- The dose of metformin HCl should be gradually escalated to reduce the gastrointestinal side effects due to metformin HCl**.**
- Empagen-M XR 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily. Empagen-M XR 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily.

2.3.2 Recommended Dosage in Patients with Renal Impairment

Assess renal function prior to initiation of Empagliflozin and Metformin HCl Extended-Release tablets and periodically, thereafter.

Empagliflozin and Metformin HCl Extended-Release tablets are contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

2.3.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Empagliflozin and Metformin HCl Extended-Release tablets 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 m^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 Empagliflozin and Metformin HCl Extended-Release tablets if renal function is stable**.**

2.3.4 Method of administration

Take Empagen-M XR orally once daily with a meal in the morning. Swallow Empagen-M 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.

2.4 Contraindication

Empagliflozin and Metformin HCl Extended-Release tablets are contraindicated in patients with:

- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), 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 or metformin HCl or to any of the excipients.

2.5 WARNINGS AND PRECAUTIONS

2.5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Empagliflozin and Metformin HCl Extended-Release tablets. In Empagliflozin and Metformin HCl Extended-Release tablets treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Empagliflozin and Metformin HCl Extended-Release tablets and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.

- Before initiating Empagliflozin and Metformin HCl Extended-Release tablets, obtain an eGFR.
- Empagliflozin and Metformin HCl Extended-Release tablets are contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking Empagliflozin and Metformin HCl Extended-Release tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of Empagliflozin and Metformin HCl Extended-Release tablets with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

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

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. Stop Empagliflozin and Metformin HCl Extended-Release tablets 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 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Empagliflozin and Metformin HCl Extended-Release tablets if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Empagliflozin and Metformin HCl Extended-Release tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Empagliflozin and Metformin HCl Extended-Release tablets**.**

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Empagliflozin and Metformin HCl Extended-Release tablets**.**

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Empagliflozin and Metformin HCl Extended-Release tablets in patients with clinical or laboratory evidence of hepatic disease.

2.5.2 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 Empagliflozin and Metformin HCl Extended-Release tablets, 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.

2.5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. Empagliflozin and Metformin HCl Extended-Release tablets are not indicated for the treatment of patients with type 1 diabetes mellitus.

Before initiating Empagliflozin and Metformin HCl Extended-Release tablets, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with Empagliflozin and Metformin HCl Extended-Release tablets consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin and Metformin HCl Extended-Release tablets in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

2.5.4 Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction and can cause renal impairment.

Renal function abnormalities can occur after initiating Empagliflozin and Metformin HCl Extended-Release tablets. Renal function should be evaluated prior to initiation of Empagliflozin and Metformin HCl Extended-Release tablets and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of Empagliflozin and Metformin HCl Extended-Release tablets is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2**.**

2.5.5 Urosepsis and Pyelonephritis

Treatment with SGLT2 inhibitors including empagliflozin increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

2.5.6 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., sulfonylureas) 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 with Empagliflozin and Metformin HCl Extended-Release tablets**.**

Metformin: 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. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Monitor for a need to lower the dose of Empagliflozin and Metformin HCl Extended-Release tablets to minimize the risk of hypoglycemia in these patients.

2.5.7 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.

2.5.8 Vitamin B_{12} Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. The decrease in vitamin B_{12} levels appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is

advised in patients on Empagliflozin and Metformin HCl Extended-Release tablets and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurement at 2-to 3-year intervals may be useful.

2.5.9 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

2.5.10 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with empagliflozin and metformin HCl extended-release combination.

2.6 USE IN SPECIFIC POPULATIONS

2.6.1 Pregnancy
Based on animal data showing adverse renal effects, Empagliflozin and Metformin HCl Extended-Release tablets are not recommended during the second and third trimesters of pregnancy.

2.6.2 Nursing Mothers
Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of Empagliflozin and Metformin HCl Extended-Release tablets is not recommended while breastfeeding.

2.6.3 Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

2.6.4 Pediatric Use
Safety and effectiveness of Empagliflozin and Metformin HCl Extended-Release tablets in pediatric patients under 18 years of age have not been established.

2.6.5 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, renal function should be assessed more frequently in elderly patients.

2.6.6 Renal impairment
Empagliflozin and Metformin HCl Extended-Release tablets are contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2).

2.6.7 Hepatic Impairment
Empagliflozin and Metformin HCl Extended-Release tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease**.**

2.7 Drug Interactions

2.7.1 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.

2.7.2 Drug Interactions with Metformin Hydrochloride
Drugs that Reduce Metformin Clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin could increase systemic exposure to metformin 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 induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Empagliflozin and Metformin HCl Extended-Release tablets 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. When such drugs are administered to a patient receiving Empagliflozin and Metformin HCl Extended-Release tablets, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin and Metformin HCl Extended-Release tablets, the patient should be observed closely for hypoglycemia.
Alcohol: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Empagliflozin and Metformin HCl Extended-Release tablets**.**

2.8 Adverse Reactions
The following important adverse reactions are described below and elsewhere in the labeling: Lactic Acidosis, Hypotension, Ketoacidosis, Acute Kidney Injury and Impairment in Renal Function, Urosepsis and Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues, Genital Mycotic Infections, Vitamin B_{12} Deficiency, Increased Low-Density Lipoprotein Cholesterol (LDL-C).

2.9 OVERDOSAGE
In the event of an overdose with Empagliflozin and Metformin HCl Extended-Release tablets, 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.

3 CLINICAL PHARMACOLOGY

3.1 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 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. 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.

3.2 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
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.

3.3 Pharmacokinetics
Empagliflozin
Absorption: After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose.
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.
Metformin hydrochloride
Absorption: Following a single oral dose of 1000 mg (2 x 500 mg 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 (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.
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.

3.3.1 Specific Populations
Renal Impairment:
Studies characterizing the pharmacokinetics of empagliflozin and metformin after administering empagliflozin and metformin extended release combination in renally impaired patients have not been performed.
Hepatic Impairment: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administering empagliflozin and metformin extended release combination in hepatically impaired patients have not been performed.
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 combination in geriatric patients have not been performed.
Pediatric
Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of empagliflozin or metformin extended release combination in pediatric patients have not been performed.

HOW SUPPLIED:
Empagen-M XR 5mg/1000mg Tablets: Alu-Alu Blister Pack of 2x7's.
Empagen-M XR 10mg/1000mg Tablets: Alu-Alu Blister Pack of 2x7's.
Empagen-M XR 12.5mg/1000mg Tablets: Alu-Alu Blister Pack of 2x7's.
Empagen-M XR 25mg/1000mg Tablets: Alu-Alu Blister Pack of 2x7's.

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:
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