4000003114

EMPAGEN TRIO

(Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets)

Product Specifications: Innovator

Empagen Trio Tablets 10mg/5mg/1000mg

Each film coated tablet contains: Empagliflozin ..... 10 mg
Linagliptin ..... 5 mg
Metformin Hydrochloride U.S.P. (as Extended Release Core) ..... 1000 mg

Empagen Trio Tablets 25mg/5mg/1000mg

Each film coated tablet contains: Empagliflozin ..... 25 mg
Linagliptin ..... 5 mg
Metformin Hydrochloride U.S.P. (as Extended Release Core) ..... 1000 mg

Empagen Trio Tablets 12.5mg/2.5mg/1000mg

Each film coated tablet contains: Empagliflozin ..... 12.5 mg
Linagliptin ..... 2.5 mg
Metformin Hydrochloride U.S.P. (as Extended Release Core) ..... 1000 mg

Empagen Trio Tablets 5mg/2.5mg/1000mg

Each film coated tablet contains: Empagliflozin ..... 5 mg
Linagliptin ..... 2.5 mg
Metformin Hydrochloride U.S.P. (as Extended Release Core) ..... 1000 mg

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

If metformin-associated lactic acidosis is suspected, immediately discontinue Empagen Trio and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

DESCRIPTION

PHARMACEUTICAL FORM:

Film Coated Tablets

Empagliflozin

Empagliflozin is an inhibitor of the SGLT2.

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.

Linagliptin

Linagliptin is an inhibitor of the DPP-4 enzyme.

Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.

Metformin

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin HCl is a white to off-white crystalline compound freely soluble in water and is practically insoluble in acetone, ether, and chloroform.

Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets)

Each film-coated tablet of *Empagen Trio* consists of an extended-release metformin hydrochloride core tablet that is coated with the immediate-release drug substances: empagliflozin and linagliptin.

Empagen Trio for oral administration are available in four strengths containing:

- 5 mg empagliflozin, 2.5 mg linagliptin, and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 10 mg empagliflozin, 5 mg linagliptin, and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 12.5 mg empagliflozin, 2.5 mg linagliptin, and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 25 mg empagliflozin, 5 mg linagliptin, and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)

CLINICAL PARTICULARS

Therapeutic indications

Empagen Trio is a combination of empagliflozin, linagliptin, and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease

Posology and method of administration

- Assess renal function before initiating Empagen Trio and as clinically indicated.
- Assess volume status. In patients with volume depletion, correct this condition before initiating Empagen Trio.

Individualize the starting dosage of Empagen Trio based on the patient's current regimen:

- In patients on metformin HCl, with or without linagliptin, switch to Empagen Trio containing a similar total daily dosage of metformin HCl and a total daily dosage of empagliflozin 10 mg and linagliptin 5 mg;
- In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to Empagen Trio containing a similar total daily dosage of metformin HCl, the same total daily dosage of empagliflozin and linagliptin 5 mg.

Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dosage of empagliflozin 25 mg, linagliptin 5 mg and metformin HCl 2,000 mg.

Take Empagen Trio tablets orally, once daily with a meal in the morning.

- Take Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) 10mg/5mg/1,000mg or Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) 25mg/5mg/1,000mg as a single tablet once daily.
- Take Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) 5mg/2.5mg/1,000mg or Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) 12.5mg/2.5mg/1,000mg as two tablets together once daily.

Swallow Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) whole. Do not split, crush, dissolve, or chew.

Renal Impairment

- Initiation of Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) is not recommended in patients with an eGFR less than 45 mL/min/1.73 m2, due to the metformin component.
- Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2 or in patients 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.

Contraindications

Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets) 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.
- Hypersensitivity to empagliflozin, linagliptin, metformin or any of the excipients in Empagen Trio (Empagliflozin, Linagliptin and Metformin HCl Extended Release Tablets), reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.

Warnings and precautions

Lactic Acidosis: 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 risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Obtain an eGFR at least annually in all patients taking Empagen Trio (Empagliflozin, Linagliptin 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.

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 Empagen Trio 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 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 Empagen Trio 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. Empagen Trio should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several 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 Empagen Trio.

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 Empagen Trio.

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 Empagen Trio in patients with clinical or laboratory evidence of hepatic disease.

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis: In patients with type 1 diabetes mellitus, empagliflozin, a component of Empagen Trio, significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including empagliflozin. Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuation of Empagen Trio; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

If ketoacidosis is suspected, discontinue Empagen Trio, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting Empagen Trio.

Pancreatitis: Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Empagen Trio and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Empagen Trio.

Volume Depletion: Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Empagen Trio in patients with one or more of these characteristics, assess volume status and renal function.

Urosepsis and Pyelonephritis: Treatment with empagliflozin increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Patients treated with Empagen Trio 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 Empagen Trio, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: Empagliflozin increases the risk for genital mycotic infections.

Lower Limb Amputations: In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Monitor patients receiving Empagen Trio for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

Severe and Disabling Arthralgia: There have been postmarketing reports of severe and disabling arthralgia in patients taking linagliptin. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. If bullous pemphigoid is suspected, Empagen Trio should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Heart Failure: An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. Consider the risks and

benefits of Empagen Trio prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy.

Use in specific populations

Pregnancy: Based on animal data showing adverse renal effects from empagliflozin, Empagen Trio is not recommended during the second and third trimesters of pregnancy. The limited available data with Empagen Trio, linagliptin, or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk.

Lactation: There is limited information regarding the presence of Empagen Trio, or its components (empagliflozin, linagliptin, 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 milk. Empagliflozin and linagliptin are present in rat milk. Since human kidney maturation occurs in utero and 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 Empagen Trio is not recommended while breastfeeding.

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.

Pediatric Use: Safety and effectiveness of Empagen Trio have not been established in pediatric patients.

Geriatric Use: Assess renal function more frequently in Empagen Trio treated geriatric patients because there is a greater risk of empagliflozin-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 Empagen Trio in geriatric patients should usually start at the lower end of the dosage range.

Drug Interactions

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 Empagen Trio may increase the risk of lactic acidosis.

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, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

Alcohol: Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. In patients with volume depletion, correct this condition before initiating Empagen Trio. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Insulin and Insulin Secretagogues: The risk of hypoglycemia is increased when Empagen Trio is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Therefore, a lower dosage of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Empagen Trio.

Drugs Affecting Glycemic Control: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

Lithium: Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

Inducers of P-glycoprotein or CYP3A4 Enzymes: Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Use of alternative treatments is strongly recommended.

Positive Urine Glucose Test: SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of fertility

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin, linagliptin, and metformin HCl.

Adverse Reactions

The following important adverse reactions are described below and elsewhere in the labeling:

Lactic Acidosis, Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis, Pancreatitis, Volume Depletion, Urosepsis and Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), Genital Mycotic Infections, Lower Limb Amputation, Hypersensitivity Reactions, Vitamin B12 Deficiency, Severe and Disabling Arthralgia, Bullous Pemphigoid, Heart Failure.

Overdosage

Lactic acidosis has been reported in approximately 32% of metformin overdose cases. 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, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action:

Empagliflozin: Empagliflozin is an inhibitor of the SGLT2, 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.

Linagliptin: Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin HCl: Metformin is an antihyperglycemic agent that 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Pharmacokinetics

Administration of Empagen Trio with food resulted in no change in overall exposure of empagliflozin or linagliptin. For metformin extended-release, high-fat meals increased systemic exposure (as measured by area- under-the-curve [AUC]) by approximately 70% relative to fasting, while Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.

Empagliflozin

Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state.

Absorption: After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition. 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%.

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.

Excretion: 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.

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).

Linagliptin

Absorption: The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced Cmax by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution: The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1,110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Elimination: Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metabolism: Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion: Following administration of an oral [14C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Metformin HCl extended-release

Absorption: Following a single oral dose of 1,000 mg (2 x 500 mg tablets) metformin HCl extended-release after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1,000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher Cmax of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin HCl extended-release from 500 mg to 2,500 mg resulted in less than proportional increase in both AUC and Cmax. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax, was not affected.

Distribution: The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination: Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

HOW SUPPLIED

Empagen Trio Tablets 10mg/5mg/1000mg:	Pack of 14 Tablets
Empagen Trio Tablets 25mg/5mg/1000mg:	Pack of 14 Tablets
Empagen Trio Tablets 12.5mg/2.5mg/1000mg:	Pack of 14 Tablets
Empagen Trio Tablets 5mg/2.5mg/1000mg:	Pack of 14 Tablets

STORAGE: Do not store above 30°C.

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

INSTRUCTIONS

Keep away from heat, light and moisture. Keep all medicines out of the reach of children.

To be sold 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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