Front

Linjardy M XR™

[Empagliflozin + Linagliptin + Metformin HCl]

TABLET

لنجارڈی ایم ایکس آر

COMPOSITION:

Linjardy M XR 5/2.5/1000 mg Tablet:
Each film coated tablet contains:
Empagliflozin ..... 5 mg.
Linagliptin ..... 2.5 mg.
(as immediate release coating)
Metformin HCl ..... 1000 mg.
(as extended release core)

Product Specs.: Innovator

Linjardy M XR 12.5/2.5/1000 mg Tablet:
Each film coated tablet contains:
Empagliflozin ..... 12.5 mg.
Linagliptin ..... 2.5 mg.
(as immediate release coating)
Metformin HCl ..... 1000 mg.
(as extended release core)

Product Specs.: Innovator

Linjardy M XR 10/5/1000 mg Tablet:
Each film coated tablet contains:
Empagliflozin ..... 10 mg.
Linagliptin ..... 5 mg.
(as immediate release coating)
Metformin HCl ..... 1000 mg.
(as extended release core)

Product Specs.: Innovator

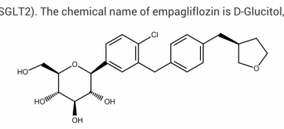
Linjardy M XR 25/5/1000 mg Tablet:
Each film coated tablet contains:
Empagliflozin ..... 25 mg.
Linagliptin ..... 5 mg.
(as immediate release coating)
Metformin HCl ..... 1000 mg.
(as extended release core)

Product Specs.: Innovator

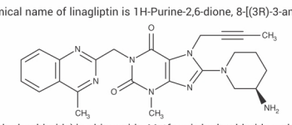
WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.
- Metformin-associated lactic acidosis has resulted in death, hypothermia, hypotension, and resistant brady-arrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory 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 and institute general supportive measures in a hospital setting. Prompt haemodialysis is recommended.

DESCRIPTION:

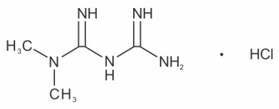
Empagliflozin: Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter (SGLT2). The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3¬ furanyl]oxy]phenyl]methyl]phenyl]-, (1S). The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



Linagliptin: Linagliptin is an inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- The molecular formula is $C_{25}H_{28}N_8O_2$ and the structural formula is:



Metformin Hydrochloride: Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin hydrochloride molecular formula is $C_4H_{11}N_5$. The structural of Metformin hydrochloride formula is:



CLINICAL PHARMACOLOGY:

Mechanism of Action:
Empagliflozin + Linagliptin + Metformin HCl XR contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a biguanide.
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.
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 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

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. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.
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 recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.
Linagliptin: Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9.
Cardiac electrophysiology: In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

Pharmacokinetics:
Administration of Empagliflozin + Linagliptin + Metformin HCl XR 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 C_{max} is not affected. Meals prolonged T_{max} by approximately 3 hours.

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 C_{max} 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%.
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. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life.
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). Systemic exposure of each metabolite was less than 10% of total drug-related material.
Excretion: Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin:
Absorption:
The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.
Distribution:
The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 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:
Absorption:
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50% to 60%.
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. 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:
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.

INDICATIONS AND USAGE:
Empagliflozin + Linagliptin + Metformin HCl XR is a combination of empagliflozin, linagliptin, and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycaemic 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

DOSAGE AND ADMINISTRATION:
Assess renal function prior to initiation of Empagliflozin + Linagliptin + Metformin HCl XR and periodically thereafter.
- In patients with volume depletion, correct this condition prior to initiation of Empagliflozin + Linagliptin + Metformin HCl XR

Recommended dose:
- Individualize the starting dose of Empagliflozin + Linagliptin + Metformin HCl XR based on the patient's current regimen:
  - In patients on metformin HCl, with or without linagliptin, switch to Empagliflozin + Linagliptin + Metformin HCl XR containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg and linagliptin 5 mg;
  - In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to Empagliflozin + Linagliptin + Metformin HCl XR containing a similar total daily dose of metformin HCl, the same total daily dose of empagliflozin and linagliptin 5 mg.
- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg, linagliptin 5 mg and metformin HCl 2000 mg.
- Take Empagliflozin + Linagliptin + Metformin HCl XR orally, once daily with a meal in the morning.
  - Take Empagliflozin + Linagliptin + Metformin HCl XR 10 mg/5 mg/1000 mg or Empagliflozin + Linagliptin + Metformin HCl XR 25 mg/5 mg/1000 mg as a single tablet once daily.
  - Take Empagliflozin + Linagliptin + Metformin HCl XR 5 mg/2.5 mg/1000 mg or Empagliflozin + Linagliptin + Metformin HCl XR 12.5 mg/2.5 mg/1000 mg as two tablets together once daily.
- Swallow Empagliflozin + Linagliptin + Metformin HCl XR tablets whole. Do not split, crush, dissolve, or chew.

Recommended dosing in renal impairment: No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m^2. Empagliflozin + Linagliptin + Metformin HCl XR should not be initiated or continued in patients with an eGFR less than 45 mL/min/1.73 m^2. Empagliflozin + Linagliptin + Metformin HCl XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.
Discontinuation for iodinated contrast imaging procedures: Discontinue Empagliflozin + Linagliptin + Metformin HCl XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 + Linagliptin + Metformin HCl XR if renal function is stable

Back

CONTRAINDICATIONS:
Empagliflozin + Linagliptin + Metformin HCl XR is contraindicated in patients with:
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), 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 Empagliflozin + Linagliptin + Metformin HCl XR, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.

ADVERSE REACTIONS:
- Lactic Acidosis
- Pancreatitis
- Heart Failure
- Hypotension
- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections

Postmarketing experience: Additional adverse reactions have been identified during post approval use of linagliptin, empagliflozin, or metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
- Acute Pancreatitis, including Fatal Pancreatitis
- Ketoacidosis
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Hypersensitivity Reactions including Anaphylaxis, Angioedema, and Exfoliative Skin Conditions
- Severe and Disabling Arthralgia
- Bullous Pemphigoid
- Skin Reactions (e.g., rash, urticaria)
- Mouth Ulceration, Stomatitis
- Cholestatic, hepatocellular, and mixed hepatocellular liver injury
- Rhabdomyolysis

- ***Lactic acidosis:*** There have been post-marketing 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; 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.
- ***Pancreatitis:*** There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue Empagliflozin + Linagliptin + Metformin HCl XR.
- ***Heart failure:*** Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of Empagliflozin + Linagliptin + Metformin HCl XR in patients who have known risk factors for heart failure. Monitor for signs and symptoms.
- ***Hypotension:*** Before initiating Empagliflozin + Linagliptin + Metformin HCl XR, assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
- ***Ketoacidosis:*** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue Empagliflozin + Linagliptin + Metformin HCl XR, evaluate and treat promptly. Before initiating Empagliflozin + Linagliptin + Metformin HCl XR, consider risk factors for ketoacidosis. Patients on Empagliflozin + Linagliptin + Metformin HCl XR may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.
- ***Acute kidney injury:*** Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.
- Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated
- ***Hypoglycemia:*** Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating Empagliflozin + Linagliptin + Metformin HCl XR.
- ***Necrotizing fasciitis of the perineum (Fournier's Gangrene):*** Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.
- ***Genital mycotic infections:*** Monitor and treat as appropriate
- ***Hypersensitivity reactions:*** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have occurred with empagliflozin and linagliptin. If hypersensitivity reactions occur, discontinue Empagliflozin + Linagliptin + Metformin HCl XR, treat promptly, and monitor until signs and symptoms resolve.
- ***Vitamin B_{12} deficiency:*** Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.
- ***Arthralgia:*** Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.
- ***Bullous pemphigoid:*** There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue Empagliflozin + Linagliptin + Metformin HCl XR.

DRUG INTERACTIONS:

Carbonic Anhydrase Inhibitors	
Clinical Impact	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.
Intervention	Concomitant use of these drugs with Empagliflozin + Linagliptin + Metformin HCl XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	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.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving Empagliflozin + Linagliptin + Metformin HCl XR.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating Empagliflozin + Linagliptin + Metformin HCl XR, 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.
Insulin or Insulin Secretagogues	
Clinical Impact	Empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue.
Intervention	When such drugs are administered to a patient receiving Empagliflozin + Linagliptin + Metformin HCl XR, the patient should be closely observed to maintain adequate glycaemic control. When such drugs are withdrawn from a patient receiving Empagliflozin + Linagliptin + Metformin HCl XR, the patient should be observed closely for hypoglycemia.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycaemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycaemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycaemic control.
Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	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.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
The limited data with Empagliflozin + Linagliptin + Metformin HCl XR and linagliptin use in pregnant women are not sufficient to inform a Linagliptin + Metformin HCl XR associated or linagliptin-associated risk for major birth defects and miscarriage. Based on animal data showing adverse renal effects from empagliflozin, Empagliflozin + Linagliptin + Metformin HCl XR is not recommended during the second and third trimesters of pregnancy.
Lactation:
There is limited information regarding the presence of Empagliflozin + Linagliptin + Metformin HCl XR or its components (linagliptin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production.
Developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Linagliptin + Metformin HCl XR and any potential adverse effects on the breastfed child from Linagliptin + Metformin HCl XR or from the underlying maternal condition.
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.
Paediatric use:
Safety and effectiveness of Empagliflozin + Linagliptin + Metformin HCl XR have not been established in paediatric patients.
Geriatric use:
Assess renal function more frequently in Empagliflozin + Linagliptin + Metformin HCl XR-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. Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.
Renal impairment:
Empagliflozin + Linagliptin + Metformin HCl XR should not be initiated or continued in patients with an eGFR less than 45 mL/min/1.73 m^2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis. The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Empagliflozin + Linagliptin + Metformin HCl XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.
Hepatic impairment:
Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Empagliflozin + Linagliptin + Metformin HCl XR is not recommended in patients with hepatic impairment.

OVERDOSAGE:
Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. 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, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected. Removal of empagliflozin by haemodialysis has not been studied, and removal of linagliptin by haemodialysis or peritoneal dialysis is unlikely.

INSTRUCTIONS:
– Store below 30°C.
– 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:
Linjardy M XR 5/2.5/1000 mg Tablet : Pack of 2 x 7 tablets.
Linjardy M XR 12.5/2.5/1000 mg Tablet : Pack of 2 x 7 tablets.
Linjardy M XR 10/5/1000 mg Tablet : Pack of 2 x 7 tablets.
Linjardy M XR 25/5/1000 mg Tablet : Pack of 2 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

3758-A
25289-0001-002-0000-0000