Emglif™-LM XR Tablets

(Empagliflozin/Linagliptin/Metformin HCl)

5mg/2.5mg/1000mg | 10mg/5mg/1000mg
12.5mg/2.5mg/1000mg | 25mg/5mg/1000mg

ایمگلِف-ایل ایم ایکس آر ٹیبلٹس

(ایمپاگلاغلوزن/لینا گلپٹن/میٹفارمن ہائیڈروکلورائیڈ)

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QUALITATIVE AND QUANTITATIVE DESCRIPTION

Emglif™-LM XR Tablet 5mg/2.5mg/1000mg
Each film coated tablet contains:
Empagliflozin (As Immediate Release).....5mg
Linagliptin (As Immediate Release).....2.5mg
Metformin Hydrochloride (U.S.P.)
(As Extended Release Core).....1000mg
Innovator's Specifications

Emglif™-LM XR Tablet 10mg/5mg/1000mg
Each film coated tablet contains:
Empagliflozin (As Immediate Release).....10mg
Linagliptin (As Immediate Release).....5mg
Metformin Hydrochloride (U.S.P.)
(As Extended Release Core).....1000mg
Innovator's Specifications

Emglif™-LM XR Tablet 12.5mg/2.5mg/1000mg
Each film coated tablet contains:
Empagliflozin (As Immediate Release)...12.5mg
Linagliptin (As Immediate Release).....2.5mg
Metformin Hydrochloride (U.S.P.)
(As Extended Release Core).....1000mg
Innovator's Specifications

Emglif™-LM XR Tablet 25mg/5mg/1000mg
Each film coated tablet contains:
Empagliflozin (As Immediate Release).....25mg
Linagliptin (As Immediate Release).....5mg
Metformin Hydrochloride (U.S.P.)
(As Extended Release Core).....1000mg
Innovator's Specifications

WARNING: LACTIC ACIDOSIS

- Post marketing cases of Metformin HCl-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmia's. The onset of Metformin HCl-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin HCl-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 HCl plasma levels generally >5 mcg/mL.
- Risk factors for Metformin HCl-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 HCl-associated lactic acidosis is suspected, immediately discontinue Empagliflozin / Metformin HCl.

DESCRIPTION

Emglif™-LM XR tablets contain three oral antihyperglycemic drugs used in the management of type 2 diabetes: Linagliptin, Empagliflozin and Met-

formin HCl.

CLINICAL PHARMACOLOGY

Mechanism of action

Linagliptin+Empagliflozin+Metformin 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.

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

At a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose, 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 activity in vitro at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

At single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), 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 LINAGLIPTIN+EMPAGLIFLOZIN+METFORMIN 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 Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.

Empagliflozin

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady-state mean plasma AUC and Cmax were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

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 faeces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in faeces 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%. 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 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

Following a single oral dose of 1000 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 1000 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 2500 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.

INDICATIONS AND USAGE

This medication 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

Recommended Dosage

• Individualize the starting dose of LINAGLIPTIN+EMPAGLIFLOZIN+METFORMIN XR based on the patient's current regimen:

1.In patients on metformin HCl, with or without linagliptin, switch to LINAGLIPTIN+EMPAGLIFLOZIN+METFORMIN XR containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg and linagliptin 5 mg;

2. In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to LINAGLIPTIN+EMPAGLIFLOZIN +METFORMIN 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 Linagliptin+Empagliflozin+Metformin XR orally, once daily with a meal in the morning.
1.Take Linagliptin+Empagliflozin+Metformin XR 10 mg/5 mg/1000 mg or Linagliptin+Empagliflozin+Metformin XR 25 mg/5 mg/1000 mg as a single tablet once daily.
2.Take Linagliptin+Empagliflozin+Metformin XR 5 mg/2.5 mg/1000mg or Linagliptin+Empagliflozin+Metformin XR 12.5 mg/2.5 mg/1000 mg as two tablets together once daily.
• Swallow Linagliptin+Empagliflozin+Metformin XR tablet whole. Do not split, crush, dissolve, or chew.
Dosage Recommendations in Patients with 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 m2. Linagliptin+Empagliflozin+Metformin XR should not be initiated or continued in patients with an eGFR less than 45 mL/min/1.73 m2. Linagliptin+Empagliflozin+Metformin XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2.

CONTRAINDICATIONS

Linagliptin+Empagliflozin+Metformin XR 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 Linagliptin+Empagliflozin+Metformin XR reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.
Other Adverse Reactions:
The following important adverse reactions are described below and elsewhere in the labelling:
• Lactic Acidosis
• Pancreatitis
• Heart Failure
• Hypotension
• Ketoacidosis
• Acute Kidney Injury
• Urosepsis and Pyelonephritis
• Hypoglycaemia with Concomitant Use with Insulin and Insulin Secretagogues
• Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
• Genital Mycotic Infections
• Hypersensitivity Reactions
• Vitamin B12 Deficiency
• Severe and Disabling Arthralgia
• Bullous Pemphigoid

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 Linagliptin+Empagliflozin+Metformin XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
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 sys-

temic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Before initiating TRIJARDY 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

Empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycaemia compared with placebo in a clinical trial. Metformin may increase the risk of hypoglycaemia when combined with insulin and/or an insulin secretagogue. Coadministration of Linagliptin+Empagliflozin+Metformin XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycaemia.

Drugs Affecting Glycaemic Control

Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving TRIJARDY XR, the patient should be closely observed to maintain adequate glycaemic control. When such drugs are withdrawn from a patient receiving TRIJARDY XR, the patient should be observed closely for hypoglycaemia.

Positive Urine Glucose Test

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.

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 when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

USE IN SPECIFIC POPULATIONS

Fertility, pregnancy and lactation

Pregnancy

Linagliptin+Empagliflozin+Metformin XR is not recommended during the second and third trimesters of pregnancy.

Lactation

Due to 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 Linagliptin+Empagliflozin+Metformin XR is not recommended while breastfeeding.

Paediatric Use

Safety and effectiveness of Linagliptin+Empagliflozin+Metformin XR in paediatric patients under 18 years of age have not been established.

Geriatric Use

Assess renal function more frequently in Linagliptin+Empagliflozin+Metformin 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. The recommended dosage of the empagliflozin and linagliptin components of Linagliptin+Empagliflozin+Metformin XR are the same in geriatric patients (patients 65 years of age

and older) as in younger adult patients. The recommended dosage for the metformin component of Linagliptin+Empagliflozin+Metformin XR in geriatric patients should usually start at the lower end of the dosage range.

Renal Impairment

Linagliptin+Empagliflozin+Metformin XR should not be initiated or continued in patients with an eGFR less than 45 mL/min/1.73 m2 and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2), end-stage renal disease, or dialysis.

Empagliflozin

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 HCl

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 in patients with hepatic impairment has been associated with some cases of lactic acidosis. Linagliptin+Empagliflozin+Metformin XR is not recommended in patients with hepatic impairment.

OVERDOSAGE

In the event of an overdose with Linagliptin+Empagliflozin+Metformin XR, contact the Poison Control Center. 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, 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.

STORAGE

Store below 30°C. Protect from light, heat and moisture. Keep all medicines out of the reach of children.

PRESENTATION

Emglif™-LM XR Tablet 5mg/2.5mg/1000mg is available in Alu/Alu blister pack of 28's.
Emglif™-LM XR Tablet 10mg/5mg/1000mg is available in Alu/Alu blister pack of 28's.
Emglif™-LM XR Tablet 12.5mg/2.5mg/1000mg is available in Alu/Alu blister pack of 28's.
Emglif™-LM XR Tablet 25mg/5mg/1000mg is available in Alu/Alu blister pack of 28's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

روشنی، گرمی اور نمی سے محفوظ رکھیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

For detailed information:

GENIX **Genix Pharma (Pvt.) Ltd.**

44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com

ISO 9001:2015 ISO 14001:2015 ISO 45001:2018

www.genixpharma.com