Diampa® LXR

(Empagliflozin + Linagliptin + Metformin HCl)

ڈائمپا ایل ایکس آر

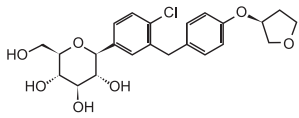
Tablets 5mg + 2.5mg + 1000mg, 10mg + 5mg + 1000mg, 12.5mg + 2.5mg + 1000mg & 25mg + 5mg + 1000mg

DESCRIPTION

Diampa L XR is a combination of Empagliflozin (a sodium-glucose cotransporter 2 (SGLT2) inhibitor), Linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor) and Metformin HCl (a biguanide), indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin

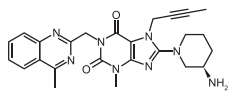
Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter (SGLT2). The chemical name of Empagliflozin is D- Glucitol,1,5- anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3 furanyl] oxy] phenyl] methyl] phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the structural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



Empagliflozin

Linagliptin

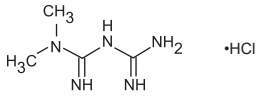
Linagliptin is an inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. The chemical name of Linagliptin is 1H-Purine-2,6-dione, 8- [(3R)-3- amino-1- piperidinyl]-7-(2-butyn-1-yl)- 3,7-dihydro-3- methyl-1- [(4-methyl- 2- quinazolinyl)methyl]. Its molecular formula is $C_{25}H_{28}N_8O_2$ and the structural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



Linagliptin

Metformin HCl

Metformin HCl (N,N-dimethylimidodicarbonimidic diamide HCl) is a biguanide. Its molecular formula is $C_4H_{11}N_5$.HCl and the structural formula is:



Metformin HCl

QUALITATIVE & QUANTITATIVE COMPOSITION

Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets are available for oral administration as:

Diampa L XR Tablets 5mg + 2.5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin…5mg
Linagliptin…2.5mg
Metformin HCl USP…1000mg
(as extended release)

Diampa L XR Tablets 10mg + 5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin…10mg
Linagliptin….5mg
Metformin HCl USP…1000mg
(as extended release)

Diampa L XR Tablets 12.5mg + 2.5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin…12.5mg
Linagliptin…2.5mg
Metformin HCl USP…1000mg
(as extended release)

Diampa L XR Tablets 25mg + 5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin…25mg
Linagliptin…5mg
Metformin HCl USP…1000mg
(as extended release)

CLINICAL PHARMACOLOGY

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.

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. 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.

Pharmacokinetics

Absorption

Empagliflozin

After oral administration, peak plasma concentrations of Empagliflozin were reached at 1.5 hours post-dose. Administration of 25mg Empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} 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.

Linagliptin

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

Metformin HCl

Following a single oral dose of 1000mg Metformin HCl extended-release after a meal, the time to reach maximum plasma Metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. 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 T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

Empagliflozin

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 [^{14}C]-Empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Linagliptin

The mean apparent volume of distribution at steady state following a single intravenous dose of Linagliptin 5mg 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 1nmol/L to 75% to 89% at ≥30nmol/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.

Metformin HCl

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

Metabolism

Empagliflozin

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. The primary route of metabolism of Empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Linagliptin

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.

Metformin HCl

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.

Elimination

Empagliflozin

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 administration of an oral [^{14}C]-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

Following administration of an oral [^{14}C]-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

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. 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.

Special Population

Patients with Renal Impairment

Empagliflozin

In patients with mild (eGFR: 60 to less than 90mL/min/1.73m^2), moderate (eGFR: 30 to less than 60mL/min/1.73m^2), and severe (eGFR: less than 30mL/min/1.73m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of Empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of Empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of Empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function.

Linagliptin

Under steady-state conditions, Linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In patients with moderate renal impairment under steady-state conditions, mean exposure of Linagliptin increased (AUC $_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in AUC$_{\tau,ss}$ by 42% and C_{max} by 35%).

Metformin HCl

In patients with decreased renal function, the plasma and blood half-life of Metformin is prolonged and the renal clearance is decreased.

Patients with Hepatic Impairment

Empagliflozin

In patients with mild, moderate, and severe hepatic impairment according to the AUC of Empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin

In patients with mild hepatic impairment steady-state exposure (AUC$_{\tau,ss}$) of Linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of Linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child- Pugh class C) had comparable exposure of Linagliptin in terms of $AUC_{0\text{-}24}$ and approximately 23% lower C_{max} compared with healthy subjects.

Metformin HCl

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

THERAPEUTIC INDICATIONS

Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) is 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.

DOSAGE & ADMINISTRATION

Testing Prior to Initiation of Diampa L XR

- Assess renal function before initiating Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) and as clinically indicated.
- Assess volume status. In patients with volume depletion, correct this condition before initiating Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl).

Recommended Dosage and Administration

Individualize the starting dose of Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets based on the patient's current regimen:

- In patients on Metformin HCl, with or without Linagliptin, switch to Diampa L XR containing a similar total daily dose of Metformin HCl and a total daily dose of Empagliflozin 10mg and Linagliptin 5mg;
- In patients on Metformin HCl and any regimen containing Empagliflozin, with or without Linagliptin, switch to Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets containing a similar total daily dose of Metformin HCl, the same total daily dose of Empagliflozin and Linagliptin 5mg.

Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of Empagliflozin 25mg, Linagliptin 5mg and Metformin HCl 2000mg.

Take Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets orally, once daily with a meal in the morning.

- Take Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 10mg + 5mg + 1000mg or Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 25mg + 5mg + 1000mg as a single tablet once daily.
- Take Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 5mg + 2.5mg + 1000mg or Diampa L XR 12.5mg + 2.5mg + 1000mg as two tablets together once daily.

Swallow Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets whole. Do not split, crush, dissolve, or chew.

Recommended Dosage in Patients with Renal Impairment

- Initiation of Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets is not recommended in patients with an eGFR less than 45mL/min/1.73m^2, due to the Metformin component.
- Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets is contraindicated in patients with an eGFR less than 30mL/min/1.73m^2 or in patients on dialysis.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60mL/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 Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets if renal function is stable.

Temporary Interruption for Surgery

Withhold Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets when the patient is clinically stable and has resumed oral intake.

Administration Instructions

Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets must be swallowed

whole and never split, crushed, dissolved, or chewed and that incompletely dissolved Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets may be eliminated in the feces.

Missed dose
Take Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Do not double the next dose.

ADVERSE REACTIONS
Following adverse reactions have been reported with the use of Empagliflozin + Linagliptin + Metformin HCl XR Tablets:
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 B_{12} deficiency, severe and disabling arthralgia, bullous pemphigoid, heart failure, upper respiratory tract infection, increased urination, dyslipidemia, nasopharyngitis, diarrhea, cough, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363."

CONTRAINDICATIONS
Empagliflozin + Linagliptin + Metformin HCl XR Tablets is contraindicated in patients with:
- Hypersensitivity to Empagliflozin, Linagliptin, Metformin HCl or to any of the excipients in of the product.
- Severe renal impairment (eGFR less than 30mL/min/1.73m^2), end-stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.

PRECAUTIONS

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 >5mcg/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. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups.
If lactic acidosis is suspected, discontinue Empagliflozin + Linagliptin + Metformin HCl XR Tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

Lactic Acidosis
There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Empagliflozin + Linagliptin + Metformin HCl XR Tablets. In Empagliflozin + Linagliptin + Metformin HCl XR 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 170mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

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 + Linagliptin + Metformin HCl XR Tablets, obtain an estimated glomerular filtration rate (eGFR). Obtain an eGFR at least annually in all patients taking Empagliflozin + Linagliptin + Metformin HCl XR Tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Geriatric Patient
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 + Linagliptin + Metformin HCl XR Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60mL/min/1.73m^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 + Linagliptin + Metformin HCl XR 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 + Linagliptin + Metformin HCl XR Tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States
Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. When such events occur, discontinue Empagliflozin + Linagliptin + Metformin HCl XR 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 + Linagliptin + Metformin HCl XR 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 + Linagliptin + Metformin HCl XR Tablets in patients with clinical or laboratory evidence of hepatic disease.

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis
Inform patients that Empagliflozin + Linagliptin + Metformin HCl XR Tablets can cause potentially fatal ketoacidosis. Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.
Withhold this product, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume Empagliflozin + Linagliptin + Metformin HCl XR Tablets when the patient is clinically stable and has resumed oral intake. Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue this product and seek medical attention immediately if signs and symptoms occur.

Acute 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 Empagliflozin + Linagliptin + Metformin HCl XR Tablets 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 Empagliflozin + Linagliptin + Metformin HCl XR Tablets.

Volume Depletion
Before initiating Empagliflozin + Linagliptin + Metformin HCl XR Tablets, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms 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 Tablets.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Empagliflozin + Linagliptin + Metformin HCl XR Tablets, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections
Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections are more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Lower Limb Amputation
In clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving Empagliflozin + Linagliptin + Metformin HCl XR Tablets 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.

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

Vitamin B_{12} Deficiency
Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities.

Severe and Disabling Arthralgia
There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. Patients experienced relief of symptoms upon discontinuation of the medication. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid
Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Inform patients to report development of blisters or erosions while receiving Empagliflozin + Linagliptin + Metformin HCl XR Tablets. If bullous pemphigoid is suspected, Empagliflozin + Linagliptin + Metformin HCl XR Tablets should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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 Tablets in patients who have known risk factors for heart failure. Monitor for signs and symptoms. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Empagliflozin + Linagliptin + Metformin HCl XR Tablets.

Effects on ability to drive and use machines
Empagliflozin + Linagliptin + Metformin HCl XR Tablets has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when this product is used in combination with other antidiabetic medicinal products known to cause hypoglycemia (e.g. insulin and analogues, sulphonylureas).

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

Nursing Mothers
Because of the potential for serious adverse reactions in a breastfed infant, including the potential for Empagliflozin to affect postnatal renal development, use of Empagliflozin + Linagliptin + Metformin HCl XR tablets is not recommended while breastfeeding.

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 Empagliflozin + Linagliptin + Metformin HCl XR Tablets 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 systemic exposure to Metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol
Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Empagliflozin + Linagliptin + Metformin HCl XR Tablets.

Diuretics
Co-administration of Empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Before initiating Empagliflozin + Linagliptin + Metformin HCl XR Tablets, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin + Linagliptin + Metformin HCl XR Tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Insulin or Insulin Secretagogues
The risk of hypoglycemia is increased when Empagliflozin + Linagliptin + Metformin HCl XR Tablets is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Coadministration of Empagliflozin + Linagliptin + Metformin HCl XR Tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Drugs Affecting Glycemic Control
Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic 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 Empagliflozin + Linagliptin + Metformin HCl XR Tablets, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin + Linagliptin + Metformin HCl XR Tablets, the patient should be observed closely for hypoglycemia.

Lithium
Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during Empagliflozin + Linagliptin + Metformin HCl XR Tablets initiation and dosage changes.

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.

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. Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

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 170mL/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. Employ clinical monitoring and institute supportive treatment as dictated by the patient's clinical status.

STORAGE
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the recommended conditions.

HOW SUPPLIED
Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 5mg + 2.5mg + 1000mg are available in pack of 14's.
Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 10mg + 5mg + 1000mg are available in pack of 14's.
Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 12.5mg + 2.5mg + 1000mg are available in pack of 14's
Diampa L XR (Empagliflozin + Linagliptin + Metformin HCl) Tablets 25mg + 5mg + 1000mg are available in pack of 14's

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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