Diampa®-M XR

ڈائمپا۔ایم ایکس آر

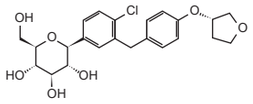
[Empagliflozin + Metformin HCl]

Extended-release Tablets
5mg + 1000mg, 10mg + 1000mg, 12.5mg + 1000mg & 25mg + 1000mg

DESCRIPTION

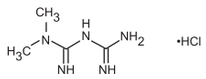
Diampa-M XR contains two oral anti-hyperglycemic drugs used in the management of type 2 diabetes: Empagliflozin and Metformin HCl.

Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). Chemically, 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

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



Metformin HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION

Diampa-M XR (Empagliflozin + Metformin HCl) Tablets is available for oral administration as:

Diampa-M XR Tablets 5mg + 1000mg
Each extended-release tablet contains:
Empagliflozin…5mg
Metformin HCl USP…1000mg

Diampa-M XR Tablets 10mg + 1000mg
Each extended-release tablet contains:
Empagliflozin…10mg
Metformin HCl USP…1000mg

Diampa-M XR Tablets 12.5mg + 1000mg
Each extended-release tablet contains:
Empagliflozin…12.5mg
Metformin HCl USP…1000mg

Diampa-M XR Tablets 25mg + 1000mg
Each extended-release tablet contains:
Empagliflozin…25mg
Metformin HCl USP…1000mg

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.

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. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacokinetics

Empagliflozin + Metformin HCl XR

Administration of Empagliflozin + Metformin HCl XR Tablets with food resulted in no change in overall exposure of empagliflozin. For metformin HCl 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

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 10mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25mg empagliflozin once daily treatment.

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

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

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. 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.

Metformin HCl

Absorption

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

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride 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

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

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, moderate and severe 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. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Metformin HCl

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease creatinine clearance.

Patients with hepatic impairment

Empagliflozin

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

Elderly

Metformin HCl

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Safety and effectiveness of Empagliflozin + Metformin HCl XR Tablets have not been established in pediatric patients.

THERAPEUTIC INDICATIONS

Diampa-M XR (Empagliflozin + 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 AND ADMINISTRATION

Prior to Initiation of Diampa-M XR (Empagliflozin + Metformin HCl)

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

Recommended Dosing

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating Diampa-M XR (Empagliflozin + Metformin HCl) Tablets.
- Individualize the starting dose of Diampa-M XR (Empagliflozin + Metformin HCl) Tablets based on the patient's current regimen:
  - In patients on metformin HCl, switch to Diampa-M XR (Empagliflozin + Metformin HCl) Tablets containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10mg.
  - In patients on empagliflozin, switch to Diampa-M XR (Empagliflozin + Metformin HCl) Tablets containing the same total daily dose of empagliflozin and a total daily dose of metformin HCl extended-release 1000mg.
  - In patients already treated with empagliflozin and metformin HCl, switch to Diampa-M XR (Empagliflozin + Metformin HCl) Tablets containing the same total daily doses of empagliflozin and a similar total daily dose of metformin HCl.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin HCl 2000mg and empagliflozin 25mg.
- The dose of metformin HCl should be gradually escalated to reduce the gastrointestinal side effects due to metformin HCl.
- Take Diampa-M XR (Empagliflozin + Metformin HCl) Tablets orally once daily with a meal in the morning.
- Swallow Diampa-M XR (Empagliflozin + Metformin HCl) Tablets whole. Do not split, crush, dissolve, or chew.

Recommended Dosage in Patients with Renal Impairment

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

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Diampa-M XR (Empagliflozin + Metformin HCl) Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73m^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-M XR (Empagliflozin + Metformin HCl) Tablets if renal function is stable.

CONTRAINDICATIONS

The combination of Empagliflozin + Metformin HCl XR Tablets is contraindicated in:

- Patients with hypersensitivity to empagliflozin , metformin HCl or to any excipient of the product.
- Moderate to severe renal impairment, end stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

Diabetic ketoacidosis should be treated with insulin.
- Diabetic pre-coma.
- Acute conditions with the potential to alter renal function such as dehydration, severe infection and shock.
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock, pulmonary embolism, acute significant blood loss, sepsis, gangrene and pancreatitis.
- During or immediately following surgery where insulin is essential and elective major surgery.
- Hepatic impairment, acute alcohol intoxication, alcoholism (due to the metformin component).
- Lactation.

ADVERSE REACTIONS

Following adverse reactions have been reported with the use of Empagliflozin + Metformin HCl XR Tablets:

Lactic acidosis, gastrointestinal symptoms, ketoacidosis, acute kidney injury, impairment in renal function, urosepsis, pyelonephritis , thirst, taste disturbance, pruritus (generalised), rash, increased urination, volume depletion, urticaria, dysuria, blood creatinine increased, glomerular filtration rate decreased, hematocrit increased, hypoglycemia with concomitant use with insulin and insulin secretagogues, genital mycotic infections, liver function tests abnormalities, hepatitis, erythema, angioedema, vitamin B12 deficiency and increased low-density lipoprotein cholesterol (LDL-C).

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

PRECAUTIONS

WARNING: LACTIC ACIDOSIS

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 Empagliflozin + Metformin HCl XR Tablets. Prompt hemodialysis is recommended.

Lactic Acidosis

Metformin HCl decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Empagliflozin + Metformin HCl XR Tablets.

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 60mL/min/1.73m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Empagliflozin + Metformin HCl XR Tablets in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin + Metformin HCl XR Tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Ketoacidosis

Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue Empagliflozin + Metformin HCl XR Tablets, evaluate and treat promptly. Before initiating Empagliflozin + Metformin HCl XR Tablets, consider risk factors for ketoacidosis. Patients on Empagliflozin + Metformin HCl XR Tablets may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

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 + Metformin HCl XR Tablets.

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

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

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., angioedema) have occurred with empagliflozin. If hypersensitivity reactions occur, discontinue Empagliflozin + Metformin HCl XR Tablets, treat promptly, and monitor until signs and symptoms resolve.

Vitamin B12 Deficiency

Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually.

Effects on ability to drive and use machines

Combination of Empagliflozin + 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 used in combination with a sulphonylurea and/or insulin.

Pregnancy

Based on available data showing adverse renal effects from empagliflozin, Empagliflozin + Metformin HCl XR Tablets is not recommended during the second and third trimesters of pregnancy. Advise females of the potential risk to a fetus especially during the second and third trimesters.

Nursing Mothers

Empagliflozin + Metformin HCl XR Tablets is not recommended when breastfeeding.

DRUG INTERACTION

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 + 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 + Metformin HCl XR Tablets.

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 Empagliflozin + Metformin HCl XR Tablets, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin + 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 is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Coadministration of Empagliflozin + Metformin HCl XR Tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses 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 + 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 + Metformin HCl XR Tablets, the patient should be observed closely for hypoglycemia.

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

Empagliflozin

Symptoms

Single doses of up to 800mg empagliflozin (equivalent to 32-times the highest recommended daily dose) in healthy subjects and multiple daily doses of up to 10mg empagliflozin (equivalent to 4-times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume.

Treatment

In the event of an overdose with empagliflozin, employ the usual supportive measures (e.g.: remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

Metformin HCl

In case of metformin HCl overdose (greater than 50g), hypoglycemia was reported in approximately 10% of cases but no causal association with metformin HCl has been established. Metformin HCl 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 HCl over dosage is suspected.

STORAGE

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

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

HOW SUPPLIED

Diampa-M XR (Empagliflozin + Metformin HCl) Tablets 5mg + 1000mg are available in pack of 14's.
Diampa-M XR (Empagliflozin + Metformin HCl) Tablets 10mg + 1000mg are available in pack of 14's.
Diampa-M XR (Empagliflozin + Metformin HCl) Tablets 12.5mg + 1000mg are available in pack of 14's.
Diampa-M XR (Empagliflozin + Metformin HCl) Tablets 25mg + 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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