

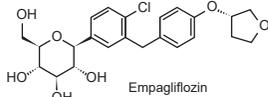
Diampa™-M

[Empagliflozin + Metformin HCl]

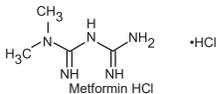
Tablets 5mg + 500mg, 5mg + 850mg, 5mg + 1000mg, 12.5mg + 500mg, 12.5mg + 850mg & 12.5mg + 1000mg

DESCRIPTION

Diampa-M 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-furanyloxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$, and the structural formula is:



Metformin HCl (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral anti-hyperglycemic agents. It has a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and the structural formula is:



QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Diampa-M Tablets 5mg + 500mg
Each film-coated tablet contains:
Empagliflozin...5mg
Metformin HCl USP...500mg

Diampa-M Tablets 5mg + 850mg
Each film-coated tablet contains:
Empagliflozin...5mg
Metformin HCl USP...850mg

Diampa-M Tablets 5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin...5mg
Metformin HCl USP...1000mg

Diampa-M Tablets 12.5mg + 500mg
Each film-coated tablet contains:
Empagliflozin...12.5mg
Metformin HCl USP...500mg

Diampa-M Tablets 12.5mg + 850mg
Each film-coated tablet contains:
Empagliflozin...12.5mg
Metformin HCl USP...850mg

Diampa-M Tablets 12.5mg + 1000mg
Each film-coated tablet contains:
Empagliflozin...12.5mg
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

It is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia. Metformin HCl stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin HCl may act via three mechanisms;

- By reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- In muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- By delaying intestinal glucose absorption.

Pharmacokinetics

Absorption

Empagliflozin

After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5 h 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 1870nmol.h and 259 nmol/L, with empagliflozin 10mg and 4740 nmol.h and 687 nmol/L with empagliflozin 25mg once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. 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.

Metformin HCl

After an oral dose of metformin HCl, T_{max} is reached in 2.5 hours. The absolute bioavailability of a single dose 500mg dose is reported to be about 50% to 60% given under fasting condition. Single oral doses of metformin HCl tablets 500mg to 1500mg, that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin HCl, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC). The pharmacokinetics of metformin HCl absorption is non-linear.

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%.

Metformin HCl

Metformin HCl is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin HCl tablets, steady-state plasma concentrations of metformin HCl are reached within 24-48 hours and are generally < 1 mcg/mL. Maximum metformin HCl plasma levels do not exceed 5mcg/mL, even at maximum doses.

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, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.

Metformin HCl

Metformin HCl is excreted unchanged in the urine and 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 hours and apparent oral clearance was 10.6 L/h. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. 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

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin HCl elimination.

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with 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.

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 HCl 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, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 46%, respectively, compared to subjects with normal hepatic function.

Metformin HCl

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

Elderly

Empagliflozin

Age did not have a clinically significant impact on the pharmacokinetics of empagliflozin.

Metformin HCl

In case of elderly patients, renal function of metformin HCl is impaired, resulting in decreased total plasma clearance, prolonged $t_{1/2}$, and increased C_{max} . So, it is recommended not to initiate empagliflozin + metformin HCl in geriatric patient unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Pediatric

Empagliflozin

No studies with empagliflozin + metformin HCl have been performed in pediatric population.

THERAPEUTIC INDICATIONS

Diampa-M (Empagliflozin + Metformin HCl) is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise:

- In patients insufficiently controlled on their maximally tolerated dose of metformin HCl alone.
- In combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin HCl and these medicinal products.
- In patients already being treated with the combination of empagliflozin and metformin HCl as separate tablets.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended dose of Diampa-M (Empagliflozin + Metformin HCl) is one tablet twice daily. The dosage should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 10mg or 25mg of empagliflozin, while not exceeding the maximum recommended daily dose of 2000mg of metformin HCl. Diampa-M (Empagliflozin + Metformin HCl) should be given with meals to reduce the gastrointestinal side effects due to metformin.

Treatment naïve patients

The recommended starting dose is 5mg + 500mg twice daily. If additional glycemic control is required, adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25mg Empagliflozin + 2000mg metformin HCl.

Patients switching from separate tablets of Empagliflozin and Metformin HCl

Patients switching from separate tablets of empagliflozin (10mg or 25mg total daily dose) and metformin HCl to Diampa-M (Empagliflozin + Metformin HCl), should receive the same daily dose of empagliflozin and metformin HCl already being taken or the nearest therapeutically appropriate dose of metformin.

Patients not adequately controlled on the maximal tolerated dose of metformin HCl alone or in combination with other products, including insulin

The recommended starting dose of Diampa-M (Empagliflozin + Metformin HCl) should provide empagliflozin 5mg twice daily (10mg total daily dose) and the dose of metformin HCl similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10mg, the dose can be increased to a total daily dose of empagliflozin 25mg.

Combination use

When Diampa-M (Empagliflozin + Metformin HCl) is used in combination with a sulphonylurea or insulin, a lower dose of sulphonylurea or insulin may be required to reduce the risk of hypoglycemia.

Special Population

Patients with renal impairment

No dose adjustment is recommended for patients with mild renal impairment. Diampa-M (Empagliflozin + Metformin HCl) is contraindicated for use in patients with moderate or severe renal impairment (creatinine clearance <60mL/min). Renal function should be assessed before initiation of treatment with metformin HCl containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Patients with Hepatic impairment

Diampa-M (Empagliflozin + Metformin HCl) must not be used in patients with hepatic impairment.

Elderly

Diampa-M (Empagliflozin + Metformin HCl) should be used with caution in elderly patients. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Due to the limited therapeutic experience with empagliflozin in patients aged 85 years and older, initiation of therapy is not recommended.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Diampa-M (Empagliflozin + Metformin HCl) at the time of or prior to an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60mL/min/1.73m², 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 and restart Diampa-M (Empagliflozin + Metformin HCl) if renal function is stable.

CONTRAINDICATIONS

The combination of Empagliflozin and Metformin HCl 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, 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, pancreatitis.
- During or immediately following surgery where insulin is essential, elective major surgery.
- Hepatic impairment, acute alcohol intoxication, alcoholism (due to the metformin component).
- Lactation.

ADVERSE REACTIONS

Very Common: Hypoglycemia (when used with sulphonylurea or insulin) and gastrointestinal symptoms.

Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection (including pyelonephritis and urosepsis), thirst, taste disturbance, pruritus (generalized), rash, increased urination and increased serum lipids.

Uncommon: Volume depletion, urticaria, dysuria, blood creatinine increased/ glomerular filtration rate decreased and hematocrit increased.

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Rare: Diabetic ketoacidosis.

Very Rare: Lactic acidosis, Vitamin B-12 deficiency, liver function tests abnormalities, hepatitis and erythema.

Not known: Necrotizing Fasciitis of the perineum (Fournier's gangrene) and Angioedema.

"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. Prompt hemodialysis is recommended.

General

Empagliflozin + Metformin HCl should not be used in patients with type 1 diabetes.

Diabetic ketoacidosis

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where diabetic ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately. Treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses. In both cases, treatment with empagliflozin may be restarted once the patient's condition has stabilized. Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Lactic Acidosis

Lactic acidosis is a serious metabolic complication, mostly occurs due to acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued.

Medicines that can acutely impair renal function (such as antihypertensive, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin HCl accumulation and an increased risk of lactic acidosis. Metformin HCl should be discontinued prior to start time of the imaging procedure and not restarted until 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction and can cause renal impairment. Before initiating empagliflozin + metformin HCl, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing empagliflozin + metformin HCl in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue empagliflozin + metformin HCl promptly and institute treatment. Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating empagliflozin + metformin HCl. Renal function should be evaluated prior to initiation of empagliflozin + metformin HCl and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73m². Use of empagliflozin + metformin HCl is contraindicated in patients with an eGFR less than 45 mL/min/1.73m².

Urosepsis and Pyelonephritis

There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

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

There have been reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue the medicine and treat promptly, and monitor until signs and symptoms resolve.

Vitamin B12 Levels

Metformin HCl may lower vitamin B12 level. Measurement of hematologic parameters on an annual basis is advised in patients on empagliflozin + metformin HCl and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurement at 2 to 3 years interval may be useful.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, empagliflozin + metformin HCl may be used with regular monitoring of cardiac and renal functions. For patients with acute and unstable heart failure, Metformin HCl is contraindicated.

Elevated hematocrit

Hematocrit increase was observed with empagliflozin treatment.

Surgery

Metformin HCl must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function is evaluated and stable.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be taken in patients for whom empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

Elderly

Effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. Therefore, special attention should be given to their volume intake in case of co-administration of drugs which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Empagliflozin + metformin HCl is not recommended in patients aged 85 years and older.

Urine laboratory assessments

Due to its mechanism of action, patients taking empagliflozin + metformin HCl will test positive for glucose in their urine.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Necrotizing fasciitis of the perineum (Fournier's gangrene) 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. Patients treated with empagliflozin + metformin HCl presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue empagliflozin + metformin HCl, closely monitor blood glucose levels and provide appropriate alternative therapy for glycemic control.

Effects on ability to drive and use machines

Combination of empagliflozin + metformin HCl 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

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with empagliflozin + metformin HCl, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus associated with abnormal blood glucose levels.

Nursing Mothers

Metformin HCl is excreted into human breast milk. It is unknown whether empagliflozin is excreted in human milk. Empagliflozin + metformin HCl should not be administered during nursing.

DRUG INTERACTIONS

Empagliflozin

Diuretics

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

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.

Metformin HCl

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.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with empagliflozin and metformin HCl may increase the risk of lactic acidosis. Frequent monitoring of these patients is required.

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 and metformin HCl, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving empagliflozin and metformin HCl, the patient should be observed closely for hypoglycemia.

Alcohol

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

Cimetidine

Reduced clearance of metformin HCl has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants

Metformin HCl increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin HCl and vitamin K antagonists are being co-administered.

Nifedipine

Co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively and increased the amount of metformin HCl excreted in the urine. Nifedipine appears to enhance the absorption of metformin HCl.

Organic Cation Transporters (OCT)

Metformin HCl is a substrate of both transporters OCT1 and OCT2. Caution should be taken especially in patients with renal impairment, when these drugs are co-administered with metformin HCl, as metformin HCl plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Glucocorticoids

Glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially after the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Insulin or Insulin Secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogues may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin + metformin HCl.

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 100mg 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

Symptoms

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. Lactic acidosis has been reported in approximately 32% of metformin HCl overdose cases.

Treatment

The most effective method to remove lactate and metformin HCl is hemodialysis. 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 (Empagliflozin + Metformin HCl) Tablets 5mg + 500mg are available in pack of 14's.

Diampa-M (Empagliflozin + Metformin HCl) Tablets 5mg + 850mg are available in pack of 14's.

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

Diampa-M (Empagliflozin + Metformin HCl) Tablets 12.5mg + 500mg are available in pack of 14's.

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Diampa-M (Empagliflozin + Metformin HCl) Tablets 12.5mg + 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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