Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Empiget-M Tablets 12.5mg + 500mg

2. Qualitative and quantitative composition

Each film-coated tablet contains:
Empagliflozin……12.5mg
Metformin HCl USP…… 500mg

3. Pharmaceutical form

Light pink colored, oblong shaped, biconvex film coated tablet, plain on both sides.

4. Clinical particulars

4.1 Therapeutic Indications

Empiget-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.

4.2 Posology and method of administration

Recommended Dosing
The recommended dose of Empiget-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 212.5mg of empagliflozin, while not exceeding the maximum recommended daily dose of 2000mg of metformin HCl. Empiget-M (Empagliflozin + Metformin HCl) should be given with meals to reduce the gastrointestinal side effects due to metformin.

Treatment naive patients
The recommended starting dose is 12.5mg+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 212.5mg Empagliflozin + 2000mg metformin HCl.

Patients switching from separate tablets of Empagliflozin and Metformin HCl
Patients switching from separate tablets of empagliflozin (10mg or 212.5mg total daily dose) and metformin HCl to Empiget-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 Empiget-M (Empagliflozin + Metformin HCl) should provide empagliflozin 12.5mg 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 212.5mg.

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

Special Populations

Patients with renal impairment
No dose adjustment is recommended for patients with mild renal impairment. Empiget-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
Empiget-M (Empagliflozin + Metformin HCl) must not be used in patients with hepatic impairment.

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

Method of administration:
Empiget-M (Empagliflozin + Metformin HCl) should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. All patients

should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet. If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken on the same time. In that case, the missed dose should be skipped.

4.3 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.

4.4 Special warnings and special precautions for use

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 >5mcg/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 stabilised. 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 accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 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/1.73 m^2. Use of empagliflozin + metformin HCl is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2.

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 B_{12} 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 may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, empagliflozin/metformin is contraindicated due to the metformin component.

Elevated hematocrit
Hematocrit increase was observed with empagliflozin treatment

Surgery
Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided hat 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 exercised 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
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the 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-administered medicinal products 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 will test positive for glucose in their urine.

4.5 Interaction with other medicinal products and other forms of 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 dichlorphenamide) 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. 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 (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at 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 hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin + metformin.

4.6 Pregnancy and Lactation

Pregnancy
When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this Empagliflozin + Metformin HC, 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.

4.7 Effects on ability to drive and use machine

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.

4.8 Undesirable effects

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 (generalised), rash, increased urination and increased serum lipids.

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

Rare
Diabetic ketoacidosis.

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

Not known
Angioedema.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdo

se

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 froms 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 overdose cases.

Treatment
The most effective method to remove lactate and metformin is haemodialysis. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs
ATC-code: A10BD20

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 a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin may act via 3 mechanisms:

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

5.2 Pharmacokinetic

properties Absorption

Empagliflozin
After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median Tmax 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 Cmax were

1870 nmol.h and 259 nmol/L with empagliflozin 10mg and 4740 nmol.h and 687 nmol/L with empagliflozin 212.5mg once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Administration of 212.5mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased by approximately 37%, compared to fasted condition.

Metformin HCl
After an oral dose of metformin HCl, Tmax 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 (Cmax), 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 the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, 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 sulfonylureas, 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 < 1mcg/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 24hours, with a plasma elimination half-life of approximately 6.2hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special population

Renal

impairment

Empagliflozin
In patients with mild, moderate or severe renal impairment (creatinine clearance <30 - <90 ml/min) and
patients with kidney failure/end stage renal disease (ESRD), 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. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in creatinine clearance 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 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.

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 Cmax. 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.

5.3 Preclinical safety data

An embryo-fetal development study in pregnant rats did not indicate a teratogenic effect attributed to the coadministration of empagliflozin and metformin at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively; and 4- times the clinical AUC exposure of metformin associated with the 2000 mg dose.
Empagliflozin Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose). Metformin hydrochloride Metformin has been studied for embryo-fetal effects in 2 rat strains and in rabbits. Metformin was not teratogenic in Sprague Dawley rats up to 600 mg/kg or in Wistar Han rats up to 200 mg/kg (2-3 times the clinical dose based on body surface area or exposure, respectively). At higher maternally toxic doses (9

and 23 times the clinical dose based on exposure), an increased incidence of rib and scapula skeletal malformations was observed in the Wistar Han strain. Metformin was not teratogenic in rabbits at doses up to 140 mg/kg (similar to clinical dose based on body surface area). Metformin administered to female Sprague Dawley rats from gestation day 6 to lactation day 21 up to 600 mg/kg/day (2 times the maximum clinical dose based on body surface area) had no effect on prenatal or postnatal development of offspring. Metformin crosses the placenta into the fetus in rats and humans.

6. Pharmaceutical particulars

6.1 List of Excipients

- Corn starch,
- Copovidone K-28
- Aerosil 200 (Colloidal Anhydrous Silica)
- Magnesium Stearate,
- Opadry Pink 04F540019

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Empiget-M (Empagliflozin + Metformin HCl) Tablets 12.5mg + 500mg are available in Alu-Alu blister packs of 4 x 7's (28's) tablets in a unit carton along with a package insert.

6.6 Special precautions for disposal and other handling#

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. Marketing authorisation holder and manufacturing site address

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900,

Pakistan Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. Marketing authorization number

CTD9094

9. Date of first authorization / renewal of the authorization

Date of first authorization: 28 April 2023

10. Date of revision of the text

11 May 2025