

For the use only of a Registered Medical Practitioner

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmia's. 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 >5 mcg/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 are provided in the Full Prescribing Information.
- If lactic acidosis is suspected, discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name & Brand Name

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets (10 mg+1000 mg)
Empixel™ - M SR 10/1000

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets (25 mg+1000 mg)
Empixel™ - M SR 25/1000

2. Qualitative and Quantitative Composition:

Empixel™ - M SR 10/1000

Each film coated tablet contains:

Empagliflozin 10 mg

Metformin Hydrochloride I.P. (as Sustained Release) 1000 mg

Excipients q.s.

Colours: Ferric Oxide USP NF Yellow, Ferric Oxide USP NF Red and Titanium Dioxide I.P.

Empixel™ - M SR 25/1000

Each film coated tablet contains:

Empagliflozin 25 mg

Metformin Hydrochloride I.P. (as Sustained Release) 1000 mg

Excipients q.s.

Colours: Indigo Carmine Aluminum Lake, Ferric Oxide USP NF Yellow and Titanium Dioxide I.P.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on a regimen containing Empagliflozin or Metformin, or in patients already being treated with both Empagliflozin and Metformin.

4.2 Posology and method of administration

Posology

Testing Prior to Initiation of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets

- Assess renal function before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and as clinically indicated.
- Assess volume status in patients with volume depletion and correct this condition before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Recommended Dosage and Administration of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in Adults

When switching to Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets from:

- Metformin HCl: initiate Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets at a similar total daily dosage of metformin HCl and a total daily empagliflozin dosage of 10 mg.
- Empagliflozin: initiate Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets at the same total daily dosage of empagliflozin and a total daily metformin HCl dosage of 1,000 mg.
- Empagliflozin and metformin HCl: initiate Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets at the same total daily dosages of each component.

Recommended dosage of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets:

- The recommended total daily dosage of empagliflozin is 10 mg.
- For additional glycemic control, empagliflozin may be increased to a maximum total daily dosage of 25 mg in patients tolerating 10 mg daily and metformin may be increased to a maximum total daily dosage of 2,000 mg, with gradual escalation to reduce gastrointestinal adverse reactions with metformin.

Dosage Recommendations in Patients with Renal Impairment

- Initiation of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets is not recommended in patients with an eGFR less than 45 mL/min/1.73 m², due to the metformin component.
- Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² or in patients on dialysis.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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; restart Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets if renal function is stable.

Method of Administration:

Take Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets orally once daily with a meal in the morning. Swallow each tablet whole. Do not split, crush, dissolve, or chew.

Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Do not double up the next dose.

4.3 Contraindications

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are contraindicated in patients with:

- severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease, or dialysis.
- acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- hypersensitivity to empagliflozin, metformin or any of the excipients in Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, reactions such as angioedema have occurred.

4.4 Special warnings and precautions for use

Lactic Acidosis

There have been post marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmia's have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin 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 and Metformin Hydrochloride (Sustained Release) Tablets. In Empagliflozin and Metformin Hydrochloride (Sustained Release) 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 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The post marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant 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. Clinical recommendations based upon the patient's renal function include:

- Before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, obtain an estimated glomerular filtration rate (eGFR).
- Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are contraindicated in patients with an eGFR below 30 mL/min/1.73 m².
- Obtain an eGFR at least annually in all patients taking Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets with specific drugs may increase the risk of metformin-associated lactic acidosis: those

that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: 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 and Metformin Hydrochloride (Sustained Release) Tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m²; 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 and Metformin Hydrochloride (Sustained Release) 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 and Metformin Hydrochloride (Sustained Release) Tablets should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) 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 and Metformin Hydrochloride (Sustained Release) 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 and Metformin Hydrochloride (Sustained Release) Tablets in patients with clinical or laboratory evidence of hepatic disease.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and post marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with Empagliflozin, and Metformin Hydrochloride (Sustained Release) Tablets may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In

some but not all cases, factors predisposing to ketoacidosis such as insulin dosage reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) 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 and Metformin Hydrochloride (Sustained Release) Tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

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

Hypoglycemia

Insulin and insulin secretagogues are known to cause hypoglycemia. In adult patients, the risk of hypoglycemia may be increased when Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. In pediatric patients aged 10 years and older, the risk of hypoglycemia was higher with empagliflozin regardless of insulin use.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

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.

Patients treated with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets 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 and Metformin Hydrochloride (Sustained Release) 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 were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions

There have been post marketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Vitamin B12 Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to-3-year intervals in patients on Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and manage any abnormalities.

4.5 Drug Interactions

Table Clinically Relevant Interactions with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets

Carbonic Anhydrase Inhibitors	
Clinical Impact	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 Hydrochloride (Sustained Release) Tablets may increase the risk of lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	

Clinical Impact	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.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of Empagliflozin and Metformin Hydrochloride (Sustained Release) 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	
Clinical Impact	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.
Intervention	When such drugs are administered to a patient receiving Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, the patient should be observed closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

Intervention	Monitor serum lithium concentration more frequently during Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	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	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from empagliflozin, Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are not recommended during the second and third trimesters of pregnancy.

The limited available data with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

In animal studies, empagliflozin, a component of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, resulted in adverse renal changes in rats when administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. No adverse developmental effects were observed when metformin was administered to pregnant rats or rabbits.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from post marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during

pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week drug-free, recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues 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 HCl: Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2,000 mg, based on body surface area (mg/m²) for rats and rabbits, respectively.

Empagliflozin and Metformin HCl: No adverse developmental effects were observed when empagliflozin and metformin HCl were co-administered to pregnant rats during the period of organogenesis 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 2,000 mg dose.

Lactation

Risk Summary

There is limited information regarding the presence of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets, or its components (empagliflozin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk (see Data). Empagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets is not recommended while breastfeeding.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants. Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5 and was greater than one from 2

to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use

Safety and effectiveness of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets have not been established in pediatric patients.

Geriatric Use

Assess renal function more frequently in Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets-treated geriatric patients because there is a greater risk of empagliflozin-associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients.

The recommended dosage for the metformin component of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in geriatric patients should usually start at the lower end of the dosage range.

Empagliflozin

In empagliflozin type 2 diabetes mellitus trials, 2,721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these trials, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

In heart failure trials, EMPEROR-Reduced included 1,188 (64%) patients treated with empagliflozin 65 years of age and older, and 503 (27%) patients 75 years of age and older. EMPEROR-Preserved included 2,402 (80%) patients treated with empagliflozin 65 years of age and older, and 1,281 (43%) patients 75 years of age and older. No overall differences in safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients.

Metformin

Clinical studies of metformin did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Renal Impairment

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m² due to the metformin component and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end stage renal disease, or dialysis.

Empagliflozin

The glucose lowering benefit of empagliflozin 25 mg decreased in adult patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. In the trial of pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, patients with an eGFR less than 60 mL/min/1.73 m² were not enrolled.

Metformin

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

Hepatic Impairment

Use of metformin HCl in patients with hepatic impairment has been associated with some cases of lactic acidosis. Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are not recommended in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets are used in combination with a Sulphonylureas and/or insulin.

4.8 Undesirable effects

The following important adverse reactions are described below and elsewhere in the labelling:

- Lactic Acidosis
- Ketoacidosis
- Volume Depletion
- Urosepsis and Pyelonephritis
- Hypoglycemia
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections
- Hypersensitivity Reactions
- Vitamin B12 Deficiency

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of concomitantly administered empagliflozin (daily dosage 10 mg or 25 mg) and metformin HCl (mean daily dosage of approximately 1,800 mg) has been evaluated in 3,456 adult patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1,271 patients received a daily dosage of empagliflozin 10 mg, and 1,259 patients received a daily dosage of empagliflozin 25 mg. Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Adverse Reactions in a Clinical Trial with Empagliflozin (Add-On Combination Therapy with Metformin and Sulphonylurea) for Glycemic Control in Adults with Type 2 Diabetes Mellitus

In a 24-week placebo-controlled trial of empagliflozin 10 mg or 25 mg administered once daily added to metformin and sulphonylurea, adverse reactions reported in $\geq 5\%$ of empagliflozin-treated patients and more commonly than in placebo-treated patients are presented in Table 1 (see also Table 4)

Table 1 Adverse Reactions Reported in $\geq 5\%$ of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin added on to Metformin plus Sulphonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Trial

Adverse Reactions	Placebo (%) n=225	Empagliflozin 10 mg (%) n=224	Empagliflozin 25 mg (%) n=217
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Hypoglycemia	9.8	15.6	12.9
Urinary tract infection	6.7	9.4	6.9
Nasopharyngitis	4.9	8.0	6.0

Empagliflozin

Clinical Trials in Adults with Type 2 Diabetes Mellitus

The data in Table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin in adult patients with type 2 diabetes mellitus. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials.

These data reflect exposure of 1,976 adult patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m²).

Table 2 shows adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in empagliflozin-treated patients than placebo-treated patients, and occurred in greater than or equal to 2% of empagliflozin-treated patients.

Table 2 Adverse Reactions Reported in ≥2% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of Empagliflozin Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	Empagliflozin 10 mg (%) N=999	Empagliflozin 25 mg (%) N=977
Urinary tract infection ^a	7.6	9.3	7.6
Female genital mycotic infections ^b	1.5	5.4	6.4
Upper respiratory tract infection	3.8	3.1	4.0
Increased urination ^c	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections ^d	0.4	3.1	1.6
Nausea	1.4	2.3	1.1

^aPredefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis ^bFemale genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal

candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), empagliflozin 10 mg (N=443), empagliflozin 25 mg (N=420). ^cPredefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia ^dMale genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials in adults, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction.

Increased Urination

In the pool of five placebo-controlled clinical trials in adults, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Hypoglycemia in Clinical Trials with Empagliflozin for Glycemic Control in Adults with Type 2 Diabetes Mellitus

The incidence of hypoglycemia in adults by trial is shown in Table 3. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

Table 3 Incidence of Overall^a and Severe^b Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus^c

Monotherapy (24 weeks)	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	Placebo + Metformin (n=206)	Empagliflozin 10 mg + Metformin (n=217)	Empagliflozin 25 mg + Metformin (n=214)
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	Placebo (n=225)	Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)	Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)
Overall (%)	8.4	16.1	11.5

Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	Placebo (n=165)	Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)	Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks ^d)	Placebo (n=170)	Empagliflozin 10 mg (n=169)	Empagliflozin 25 mg (n=155)
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks ^d)	Placebo (n=188)	Empagliflozin 10 mg (n=186)	Empagliflozin 25 mg (n=189)
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

aOverall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL bSevere hypoglycemic events: requiring assistance regardless of blood glucose cTreated set (patients who had received at least one dosage of trial drug) ^dInsulin dosage could not be adjusted during the initial 18-week treatment period

Other Adverse Reactions in Clinical Trials with Empagliflozin for Glycemic Control in Adults with Type 2 Diabetes Mellitus

- Genital Mycotic Infections:** In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 or 25 mg.
 Genital mycotic infections occurred more frequently in female than male patients (see Table 2).
 Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).
- Urinary Tract Infections:** In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared to placebo (see Table 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.
 Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25

mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively.

Clinical Trial of Empagliflozin in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus

Empagliflozin was administered to 52 patients in a trial of 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus with a mean exposure to empagliflozin of 23.8 weeks [see Clinical Studies (14.2)]. Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m² and mean BMI Zscore was 3.0. Approximately 25% of the trial population had microalbuminuria or macroalbuminuria.

The risk of hypoglycemia was higher in pediatric patients treated with empagliflozin regardless of concomitant insulin use. Hypoglycemia, defined as a blood glucose < 54 mg/dL, occurred in 10 (19.2%) patients and in 4 (7.5%) patients treated with empagliflozin and placebo, respectively. No severe hypoglycemic events occurred (severe hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions).

Adverse Reactions with Clinical Trials of Metformin

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%).

Pediatric Patients

In clinical trials with metformin HCl immediate-release tablets in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin or Metformin

Empagliflozin

- **Increases in Serum Creatinine and Decreases in eGFR:** Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of adults with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m², respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.
- **Increase in Low-Density Lipoprotein Cholesterol (LDL-C):** Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in adults treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.
- **Increase in Hematocrit:** In a pool of four placebo-controlled trials in adults, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg-treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients

with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Metformin

- Decrease in Vitamin B12: In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

Post marketing Experience

Additional adverse reactions have been identified during post approval use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Empagliflozin

- Gastrointestinal Disorders: Constipation
- Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis
- Metabolism and Nutrition Disorders: Ketoacidosis Renal and Urinary Disorders: Acute kidney injury
- Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin HCl

- Hepatobiliary Disorders: Cholestatic, hepatocellular, and mixed hepatocellular liver injury

4.9 Overdose

Symptoms

Empagliflozin

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32-times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg 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. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

Metformin

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital (see sections 4.4 and 4.5).

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis. The removal of empagliflozin by haemodialysis has not been studied.

5. Pharmacological properties

5.1 Mechanism of action

Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets contain: empagliflozin, a SGLT2 inhibitor, and metformin, a biguanide.

Empagliflozin

Empagliflozin is an inhibitor of the SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions such as lowering both pre-and afterload of the heart and downregulating sympathetic activity.

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 SUs, 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 decrease.

5.2 Pharmacodynamic Properties

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily [see Clinical Studies (14)]. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

5.3 Pharmacokinetic properties

Administration of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets with food resulted in no change in overall exposure of empagliflozin. For metformin HCl extended-release high-fat meals increased systemic exposure to metformin (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

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steady state mean plasma AUC and C_{max} were 1,870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Empagliflozin does not appear to have time-dependent

pharmacokinetic characteristics. Following once daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Administration of 25 mg 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.

Distribution

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

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

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'-diphosphoglucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

Following administration of an oral [¹⁴C]-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 extended release

Absorption

Following a single oral dose of 1,000 mg (2 x 500 mg tablets) 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. In both single- and multiple-dose studies in healthy subjects, once daily 1,000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin HCl extended release from 500 mg to 2,500 mg resulted in less than proportional increase in both AUC and C_{max}. 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 HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism

Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion

Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Bioequivalence study data

An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, two-way crossover design, oral bioequivalence study comparing Empixel™ M 25/1000 [Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets (25 mg+1000 mg)] of Abbott Healthcare Pvt. Ltd., India (Test Product) with Synjardy XR tablet of Boehringer Ingelheim Pharmaceuticals, Inc., (Reference Product) was conducted in healthy, adult, human subjects under fasting conditions.

The 90% confidence intervals of the ratio of geometric least squares means of Ln-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Empagliflozin and Metformin were within the bioequivalence acceptance limits of 80.00 - 125.00%. The results of the study demonstrated that the test product Empixel™ M 25/1000 [Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets (25 mg+1000 mg)] and reference product Synjardy XR tablet were bioequivalent with respect to rate and extent of absorption.

Specific Populations

Pediatric Patients

Empagliflozin

The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

Metformin

After administration of a single oral metformin HCl 500 mg immediate-release tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin

Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Metformin HCl

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Patients with Hepatic Impairment

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in hepatically impaired patients have not been performed.

Empagliflozin

In adult patients with mild, moderate, and severe hepatic impairment according to the ChildPugh classification, 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.

Metformin HCl

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

Patients with Renal Impairment

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in renally impaired patients have not been performed.

Empagliflozin

In adult patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) renal impairment and patients on dialysis due to kidney failure, 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 patients with moderate renal impairment and patients on dialysis due to kidney failure, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients 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

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

Geriatric

Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets in geriatric patients have not been performed.

Empagliflozin

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis.

Metformin HCl

Limited data from controlled pharmacokinetic studies of metformin HCl 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and metformin HCl. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and metformin.

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100,

300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the in vitro Ames bacterial mutagenicity assay, the in vitro L5178Y tk⁺/– mouse lymphoma cell assay, and an in vivo micronucleus assay in rats.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Metformin HCl

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

7. Description

Empixel™ - M SR 10/1000 is supplied for oral administration, as film coated tablet of Empagliflozin and Metformin Hydrochloride I.P. (as Sustained Release). Each film coated tablet of Empixel™ - M SR 10/1000 contains Empagliflozin 10 mg and Metformin Hydrochloride I.P. (as Sustained Release) 1000 mg.

Empixel™ - M SR 25/1000 is supplied for oral administration, as film coated tablet of Empagliflozin and Metformin Hydrochloride I.P. (as Sustained Release). Each film coated tablet of Empixel™ - M SR 25/1000 contains Empagliflozin 25 mg and Metformin Hydrochloride I.P. (as Sustained Release) 1000 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

NA

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack.

8.4 Storage condition & Handling instructions

Refer Pack.

9. Patient Counseling Information

Advise the patient to read the approved patient labeling (Medication Guide).

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to metformin, its symptoms, and conditions that predispose to its development. Advise patients to discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets immediately and to notify their healthcare provider promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. Instruct patients to inform their healthcare provider that they are taking Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets prior to any surgical or radiological procedure, as temporary discontinuation may be required until renal function has been confirmed to be normal.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and seek medical attention immediately.

Volume Depletion

Inform patients that symptomatic hypotension may occur with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets and advise them to contact their healthcare provider if they experience such symptoms. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Hypoglycemia

Inform patients that hypoglycemia has been reported when Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets is used with insulin secretagogues or insulin. Hypoglycemia may occur in pediatric patients regardless of concomitant antidiabetic treatment. Educate patients or caregivers on the signs and symptoms of hypoglycemia.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin, a component of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with empagliflozin, a component of Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. Advise patients to report immediately any skin reaction or angioedema, and to discontinue the drug until they have consulted prescribing healthcare provider.

Vitamin B12 Deficiency

Inform patients about the importance of regular hematological parameters while receiving Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Pregnancy

Advise pregnant patients, and patients of reproductive potential, of the potential risk to a fetus with treatment with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets. Instruct patients to report pregnancies to their healthcare provider as soon as possible.

Lactation

Advise patients that breastfeeding is not recommended during treatment with Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets.

Patients of Reproductive Potential

Inform patients that treatment with metformin may result in ovulation in some premenopausal anovulatory patients, which may lead to unintended pregnancy.

Administration Instructions

Inform patients that Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets tablets must be swallowed whole and never split, crushed, dissolved, or chewed and that incompletely dissolved Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets tablets may be eliminated in the feces.

Missed Dose

Instruct patients to take Empagliflozin and Metformin Hydrochloride (Sustained Release) Tablets only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

10. Details of manufacturer

Refer Pack for manufacturer details.

11. Details of permission or licence number with date

Refer Pack for Permission/License details.

12. Date of revision

Version 2.0, dated 20/12/2024

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