Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Empagliflozin and Metformin hydrochloride extended-release tablets 5 mg/1000 mg

2. Qualitative and quantitative composition:

Empagliflozin and metformin hydrochloride extended-release tablets 10 mg/1000 mg

Each extended- release tablet contains:
Empagliflozin ....10 mg
and Metformin Hydrochloride USP   1000 mg

3. Pharmaceutical form:

Extended-release tablets

<u>Product description</u>

Empagliflozin and metformin hydrochloride extended-release tablets 10 mg/1000 mg

Dark pink, oval shaped, film coated tablet, printed on one side with C586 and plain on other side.

4. Clinical particulars:
4.1. Therapeutic indications:

Empagliflozin and metformin hydrochloride extended-release tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease (see section 5.1). However, the effectiveness of empagliflozin and metformin hydrochloride extended-release tablets on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

<u>Limitations of Use</u>

Empagliflozin and metformin hydrochloride extended-release tablets is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (see section 4.4).

4.2. Posology and method of administration:

Recommended Dosage

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating empagliflozin and metformin hydrochloride extended- release tablets (see section 4.4).
- Individualize the starting dose of empagliflozin and metformin hydrochloride extended-release tablets based on the patient's current regimen:

  - In patients on metformin hydrochloride, switch to empagliflozin and metformin hydrochloride extended-release tablets containing a similar total daily dose of metformin hydrochloride and a total daily dose of empagliflozin 10 mg;
  - In patients on empagliflozin, switch to empagliflozin and metformin hydrochloride extended-release tablets containing the same total daily dose of empagliflozin and a total daily dose of metformin hydrochloride extended-release 1000 mg;
  - In patients already treated with empagliflozin and metformin hydrochloride, switch to empagliflozin and metformin hydrochloride extended-release tablets containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg *(see below)*.
- The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride.
- Take empagliflozin and metformin hydrochloride extended-release tablets orally once daily with a meal in the morning
- Swallow empagliflozin and metformin hydrochloride extended-release tablets whole. Do not split, crush, dissolve, or chew before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin hydrochloride extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control.
- Empagliflozin and metformin hydrochloride extended-release tablets 10 mg/1000 mg and 25 mg/1000 mg should be taken as a single tablet

once daily. Empagliflozin and metformin hydrochloride extended-release tablets 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily.

Recommended Dosage in Patients with Renal Impairment

- Assess renal function prior to initiation of empagliflozin and metformin hydrochloride extended-release tablets and periodically, thereafter.
- Empagliflozin and metformin hydrochloride extended-release tablets are contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2 (see section 4.3 and 4.4).

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue empagliflozin and metformin hydrochloride extended-release tablets at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart empagliflozin and metformin hydrochloride extended-release tablets if renal function is stable (see section 4.4).

4.3. Contraindications:

Empagliflozin and metformin hydrochloride extended-release tablets is contraindicated in patients with:
- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), end stage renal disease, or dialysis (see sections 4.4 and 5.1).
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin (see section 4.4).
- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients in empagliflozin and metformin
- hydrochloride extended-release tablets.

4.4. Special warnings and precautions for use:

Lactic Acidosis

There have been postmarketing 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 bradyarrhythmias 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. In empagliflozin and metformin hydrochloride
-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 extended-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 postmarketing 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 (see section 4.2 and 5.2).

- Before initiating empagliflozin and metformin hydrochloride, obtain an estimated glomerular filtration rate (eGFR).
- Empagliflozin and metformin hydrochloride extended-release tablets are contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2 (see section 4.3).
- Obtain an eGFR at least annually in all patients taking empagliflozin and metformin hydrochloride extended-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 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 (see section 4.5). 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 (see section 5.1).

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 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 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re- evaluate eGFR 48 hours after the imaging procedure, and restart empagliflozin and metformin hydrochloride 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 should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing 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.

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.

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 in patients with clinical or laboratory evidence of hepatic disease.

Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin (see section 4.8) particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating empagliflozin and metformin hydrochloride, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected (see section 5.1).

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing 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. Empagliflozin and metformin hydrochloride are not indicated for the treatment of patients with type 1 diabetes mellitus (see section 4.1).

Patients treated with empagliflozin and metformin hydrochloride 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 may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, empagliflozin and metformin hydrochloride 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 postmarketing 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 dose reduction, acute febrile illness, reduced caloric intake due to illness or 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, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with empagliflozin and metformin hydrochloride consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin and metformin hydrochloride in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction (see section 4.4) and can cause renal impairment (see section 4.8). There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating empagliflozin and metformin hydrochloride, 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 and metformin hydrochloride 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 and metformin hydrochloride 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 and metformin hydrochloride (see section 4.8). Renal function should be evaluated prior to initiation of empagliflozin and metformin hydrochloride and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m². Use of empagliflozin and metformin hydrochloride is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m² (see sections 4.2, 4.3 and 5.1).

Urosepsis and Pyelonephritis

There have been postmarketing 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 (see section 4.8).

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Empagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin (see section 4.8). Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin and metformin hydrochloride.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs. Monitor for a need to lower the dose of empagliflozin and metformin hydrochloride to minimize the risk of hypoglycemia in these patients.

Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections (see section 4.8). 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 postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin, one of the components of empagliflozin and metformin hydrochloride extended-release tablets. If a hypersensitivity reaction occurs, discontinue empagliflozin and metformin hydrochloride extended-release tablets; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin and metformin hydrochloride extended-release tablets are contraindicated in patients with a previous serious hypersensitivity reaction to empagliflozin or any of the excipients in empagliflozin and metformin hydrochloride extended-release tablets (see section 4.3).

Vitamin B12 Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B12 levels appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on empagliflozin and metformin hydrochloride 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-year intervals may be useful.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

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

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with empagliflozin and metformin hydrochloride.

4.5. Interaction with other medicinal products and other forms of interaction

Drug Interactions with Empagliflozin

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion (see section 4.4).

Insulin or Insulin Secretagogues

Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycaemia (see section 4.4).

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. Use alternative methods to monitor glycemic control.

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. Use alternative methods to monitor glycemic control.

Drug Interactions with Metformin Hydrochloride

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 (see section 5.2). 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 hydrochloride may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients (see sections 4.4 and 5.2).

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 hydrochloride, the patient should be closely observed to maintain adequate glycemic control (see section 5.2). When

such drugs are withdrawn from a patient receiving empagliflozin and metformin hydrochloride, the patient should be observed closely for hypoglycemia.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving empagliflozin and metformin hydrochloride extended-release tablets.

4.6. Fertility, Pregnancy and lactation

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, empagliflozin and metformin hydrochloride extended-release tablets are not recommended during the second and third trimesters of pregnancy.

Limited available data with empagliflozin and metformin hydrochloride extended-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 *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal changes were observed in rats when empagliflozin was 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. Empagliflozin was not teratogenic 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 when administered during organogenesis. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits

during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area *(see Data).*

The estimated background risk of major birth defects is 6-10% in women with pre- gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% 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 2-4% and 15- 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, stillbirth, 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 hydrochloride: Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at 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 2000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively.

Empagliflozin and Metformin hydrochloride: No adverse developmental effects were observed when empagliflozin and metformin hydrochloride were coadministered 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 2000 mg dose.

Lactation

Risk Summary

There is no information regarding the presence of empagliflozin and metformin hydrochloride or empagliflozin 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)*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Empagliflozin is present in the milk of lactating rats *(see Data)*. 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 women that use of empagliflozin and metformin hydrochloride extended-release tablets are 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 -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.

Fertility

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

4.7. Effects on ability to drive and use machines

Empagliflozin and metformin hydrochloride extended-release tablets have 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 extended-release tablets are used in combination with a sulphonylurea and/or insulin.

4.8. Undesirable effects:

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

- Lactic Acidosis (see section 4.4)
- Hypotension (see section 4.4)
- Ketoacidosis (see section 4.4)
- Acute Kidney Injury and Impairment in Renal Function (see section 4.4)
- Urosepsis and Pyelonephritis (see section 4.4)
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues (see section 4.4)
- Genital Mycotic Infections (see section 4.4)
- Hypersensitivity Reactions (see section 4.4)
- Vitamin B12 Deficiency (see section 4.4)
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) (see section 4.4)

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 dose 10 mg and 25 mg) and metformin hydrochloride (mean daily dose of approximately 1800 mg) has been evaluated in 3456 patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1271 patients received a daily dose of empagliflozin 10 mg, and 1259 patients received a daily dose 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.

Empagliflozin Add-On Combination Therapy with Metformin

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin, there were no adverse reactions reported regardless of

investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo are presented in Table 1 (see also Table 4).

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin added on to Metformin plus Sulfonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Study

	Number (%) of Patients		
	Placebo n=225	**Empagliflozin 10 mg n=224**	**Empagliflozin 25 mg n=217**
Hypoglycemia	22 (9.8)	35 (15.6)	28 (12.9)
Urinary tract infection	15 (6.7)	21 (9.4)	15 (6.9)
Nasopharyngitis	11 (4.9)	18 (8.0)	13 (6.0)

Empagliflozin

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. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials *(see Clinical Studies).*

These data reflect exposure of 1976 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 common adverse reactions (excluding hypoglycemia) associated with the use of empagliflozin. The adverse reactions were not present at baseline, occurred more commonly on empagliflozin than on placebo and occurred in greater than or equal to 2% of patients treated with empagliflozin 10 mg or empagliflozin 25 mg.

Table 2 Adverse Reactions Reported in ≥2% of Patients Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of Empagliflozin Monotherapy or Combination Therapy

	Number (%) of Patients		
	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%

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[b]Female 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).
[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[d]Male 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, 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 (see sections 4.4 and 5.1).

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 3). 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.

Acute Impairment in Renal Function

Treatment with empagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 3). Patients with moderate renal impairment at baseline had larger mean changes (see sections 4.4 and 5.1).

In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

Table 3 Changes from Baseline in Serum Creatinine and eGFR[a] in the Pool of Four 24- week Placebo-Controlled Studies and Renal Impairment Study

	Pool of 24-Week Placebo-Controlled Studies

		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Baseline Mean	N	825	830	822
	Creatinine (mg/dL)	0.84	0.85	0.85
	eGFR (mL/min/1.73 m^2)	87.3	87.1	87.8
Week 12 Change	N	771	797	783
	Creatinine (mg/dL)	0.00	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-1.3	-1.4
Week 24 Change	N	708	769	754
	Creatinine (mg/dL)	0.00	0.01	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-0.6	-1.4

		Moderate Renal Impairment[b]		
		Placebo		Empagliflozin 25 mg
Baseline Mean	N	187	-	187
	Creatinine (mg/dL)	1.49	-	1.46
	eGFR (mL/min/1.73 m^2)	44.3	-	45.4
Week 12 Change	N	176	-	179
	Creatinine (mg/dL)	0.01	-	0.12
	eGFR (mL/min/1.73 m^2)	0.1	-	-3.8
Week 24 Change	N	170	-	171
	Creatinine (mg/dL)	0.01	-	0.10
	eGFR (mL/min/1.73 m^2)	0.2	-	-3.2
Week 52 Change	N	164	-	162
	Creatinine (mg/dL)	0.02	-	0.11
	eGFR (mL/min/1.73 m^2)	-0.3	-	-2.8
Post-treatment Change[c]	N	98	-	103
	Creatinine (mg/dL)	0.03	-	0.02
	eGFR (mL/min/1.73 m^2)	0.16	-	1.48

[a]Observed cases on treatment.
[b]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2.
[c]Approximately 3 weeks after end of treatment.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 4. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea (see section 4.4).

Table 4 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[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%

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

[c]Treated set (patients who had received at least one dose of study drug)

[d]Insulin dose could not be adjusted during the initial 18 week treatment period

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 study 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 (see sections 4.4 and 5.1).

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%).

Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anemia) (see section 4.4).

Laboratory Tests

Empagliflozin

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low- density lipoprotein cholesterol (LDL-C) were observed in patients 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 (see section 4.4). 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 studies, 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

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation (see section 4.4).

Postmarketing Experience

Additional adverse reactions have been identified during postapproval 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

- Ketoacidosis (see section 4.4)
- Urosepsis and pyelonephritis (see section 4.4)
- Angioedema (see section 4.4)
- Skin reactions (e.g., rash, urticaria)

Metformin hydrochloride

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

Reporting of suspected adverse reactions

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. Overdose:

In the event of an overdose with empagliflozin and metformin hydrochloride, e mploy the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom empagliflozin and metformin hydrochloride overdosage is suspected.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see section 4.4).

5. Pharmacological properties:
5.1. Pharmacodynamic properties:

Mechanism of Action

Empagliflozin and metformin hydrochloride extended-release tablets

Empagliflozin and metformin hydrochloride extended-release tablets combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a member of the biguanide class.

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 hydrochloride

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) (see section 4.4) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, 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)*.

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.

Pediatric Use

Safety and effectiveness of empagliflozin and metformin hydrochloride in pediatric patients under 18 years of age have not been established.

Geriatric Use

Because renal function abnormalities can occur after initiating

empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients (see sections 4.2 and 4.4).

Empagliflozin

No empagliflozin dosage change is recommended based on age (see section 4.2). In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and
empagliflozin 25 mg, respectively (see sections 4.4 and 4.8).

Metformin hydrochloride

Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients (see sections 4.3, 4.4 and 5.2).

Renal Impairment

Empagliflozin and metformin hydrochloride extended-release tablets are contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2).

Empagliflozin

The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations (see sections 4.2, 4.3 and 4.4).

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment (see section 4.4), volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Empagliflozin may be used in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2 (see section 5.2). Empagliflozin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2.

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Empagliflozin and metformin hydrochloride extended-release tablets are contraindicated in moderate to severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 (see sections 4.3 and 4.4).

Hepatic Impairment

Empagliflozin and metformin hydrochloride extended-release tablets should generally be avoided in patients with clinical or laboratory evidence of hepatic disease (see section 4.4).

Empagliflozin

Empagliflozin may be used in patients with hepatic impairment (see section 5.2).

Metformin hydrochloride

Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. Empagliflozin and metformin hydrochloride extended- release tablets are not recommended in patients with hepatic impairment (see section 4.4).

CLINICAL STUDIES

Empagliflozin and Metformin Hydrochloride Extended-Release Tablets Glycemic Control Studies

In patients with type 2 diabetes, treatment with empagliflozin and metformin produced clinically and statistically significant improvements in HbA1c compared to placebo. Reductions in HbA1c were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

Empagliflozin Add-On Combination Therapy with Metformin

A total of 637 patients with type 2 diabetes participated in a double-blind, placebo- controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin hydrochloride per day entered an open-label 2-week placebo run-in. At the end of the run-in

period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

At Week 24, treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 5).

Table 5 Results at Week 24 From a Placebo-Controlled Study for Empagliflozin used in Combination with Metformin

	Empagliflozin 10 mg + Metformin N=217	Empagliflozin 25 mg + Metformin N=213	Placebo + Metformin N=207
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6[b] (-0.7, -0.4)	-0.6[b] (-0.8, -0.5)	-
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)[c]			
Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	-
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0[b] (-2.6, -1.4)	-2.5[b] (-3.1, -1.9)	-

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for empagliflozin 10 mg, n=216, for empagliflozin 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 10 mg and -

4.8 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 25 mg.

Empagliflozin Initial Combination Therapy with Metformin

A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized to one of 8 active-treatment arms: empagliflozin 10 mg or 25 mg; metformin hydrochloride 1000 mg, or 2000 mg; empagliflozin 10 mg in combination with 1000 mg or 2000 mg metformin; or empagliflozin 25 mg in combination with 1000 mg or 2000 mg metformin hydrochloride.

At Week 24, initial therapy of empagliflozin in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 6).

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing Empagliflozin and Metformin to the Individual Components as Initial Therapy

	Empagliflozin 10 mg + Metformin 1000 mg[a] N=161	Empagliflozin 10 mg + Metformin 2000 mg[a] N=167	Empagliflozin 25 mg + Metformin 1000 mg[a] N=165	Empagliflozin 25 mg + Metformin 2000 mg[a] N=169	Empagliflozin 10 mg N=169	Empagliflozin 25 mg N=163	Metformin 1000 mg[a] N=167	Metformin 2000 mg[a] N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs	-0.6[b] (-0.9,	-0.7[b] (-1.0,	-0.6[c] (-0.8, -	-0.7[c] (-1.0, -	-	-	-	-

empagliflozin (adjusted mean) (95% CI)	- 0.4)	- 0.5)	0.3)	0.5)				
Comparison vs metformin (adjusted mean) (95% CI)	- 0.8[b] (-1.0, - 0.6)	- 0.3[b] (-0.6, - 0.1)	-0.8[c] (-1.0, - 0.5)	-0.3[c] (-0.6, - 0.1)	-	-	-	-
Patients [n (%)] achieving HbA1c <7%	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

[a]Metformin hydrochloride total daily dose, administered in two equally divided doses per day.

[b]p-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

[c]p-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

A total of 666 patients with type 2 diabetes participated in a double-blind, placebo- controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin hydrochloride and on a sulfonylurea, entered a 2-week open-label placebo run- in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

Treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 7).

Table 7 Results at Week 24 from a Placebo-Controlled Study for Empagliflozin in Combination with Metformin and Sulfonylurea

	Empagliflozin 10 mg + Metformin + SU N=225	Empagliflozin 25 mg + Metformin + SU N=216	Placebo + Metformin + SU N=225
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline	-0.8	-0.8	-0.2

(adjusted mean)			
Difference from placebo (adjusted mean) (95% CI)	-0.6[b] (-0.8, -0.5)	-0.6[b] (-0.7, -0.4)	-
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)[c]			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	-
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo	-2.4[b] (-3.0, -1.8)	-2.7[b] (-3.3, -2.1)	-
(adjusted mean) (95% CI)			

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively. [b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for empagliflozin 10 mg, n=225, for empagliflozin 25 mg, n=215, for placebo, n=224

Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of empagliflozin was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2- week run-in period were randomized to glimepiride or empagliflozin 25 mg.

At Week 52, empagliflozin 25 mg and glimepiride lowered HbA1c and FPG (see Table 8, Figure 1). The difference in observed effect size between empagliflozin 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

Table 8 Results at Week 52 from an Active-Controlled Study Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

|	Empagliflozin 25 mg + Metformin N=765	Glimepiride + Metformin N=780
HbA1c (%)[a]		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07[b] (-0.15, 0.01)	-
FPG (mg/dL)[d]		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9[c] (-6.3, -5.5)	

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to empagliflozin 25 mg and glimepiride, respectively.
[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)
[c]ANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[d]FPG (mg/dL); for empagliflozin 25 mg, n=764, for placebo, n=779

Figure 1 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF
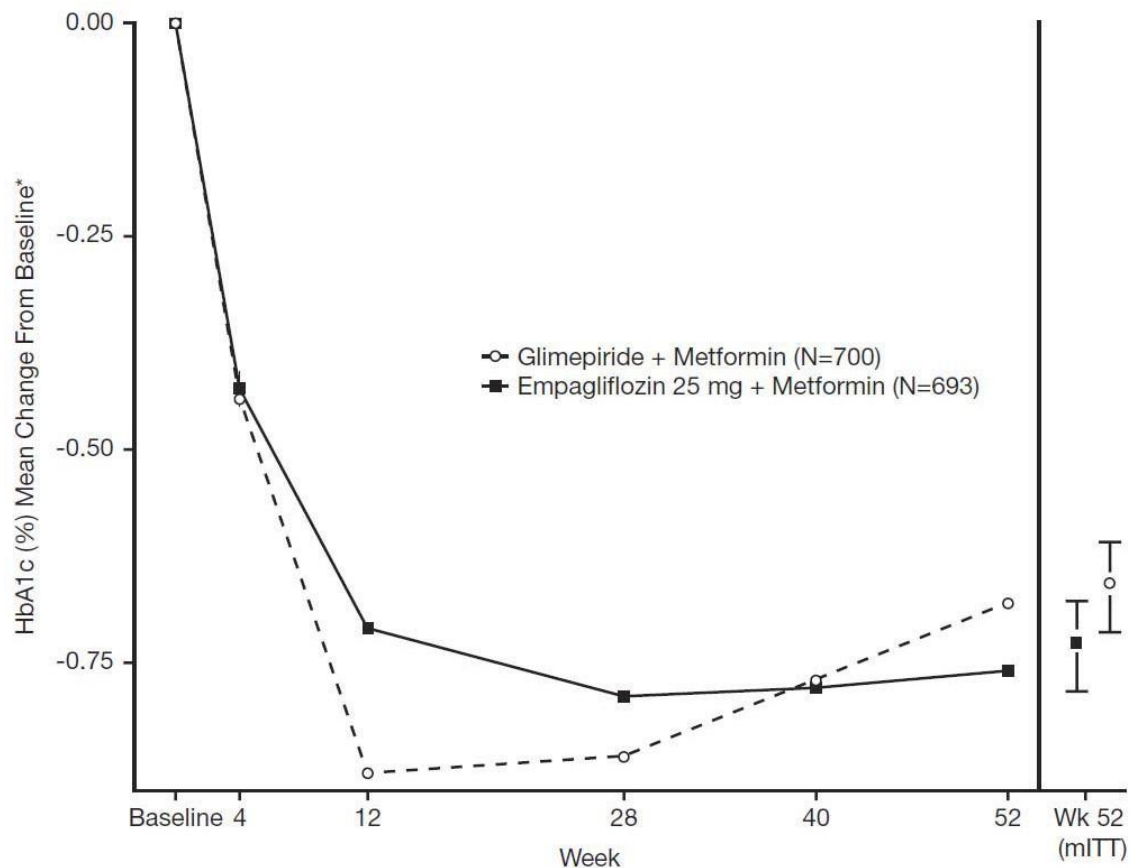
*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for empagliflozin 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-

specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for empagliflozin 25 mg and 12.9% for glimepiride.

At Week 104, empagliflozin 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for empagliflozin 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

Empagliflozin Cardiovascular Outcome Study in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of empagliflozin and metformin hydrochloride extended-release tablets on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has not been established. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

The EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double- blind parallel group trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following; a documented history of coronary artery disease

(76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 9 and Figure 2 and 3). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 9 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	Empagliflozin N=4687	Hazard ratio vs placebo (95% CI)
Composite of cardiovascular death, non-fatal myocardial infarction, non- fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

[a]Treated set (patients who had received at least one dose of study drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

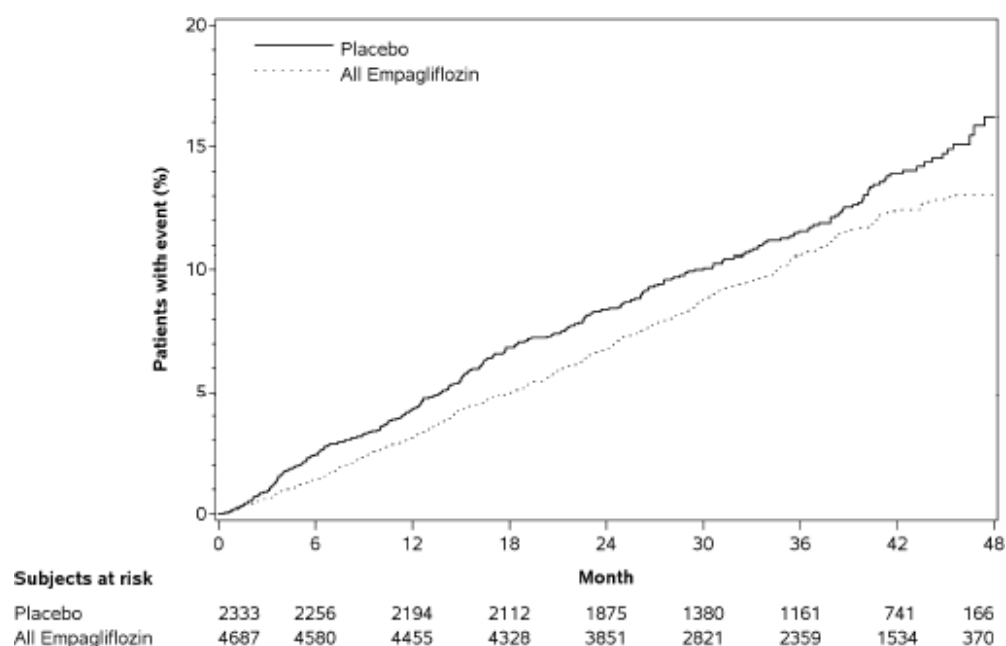**Figure 2 Estimated Cumulative Incidence of First MACE**

Figure 3 Estimated Cumulative Incidence of Cardiovascular Death
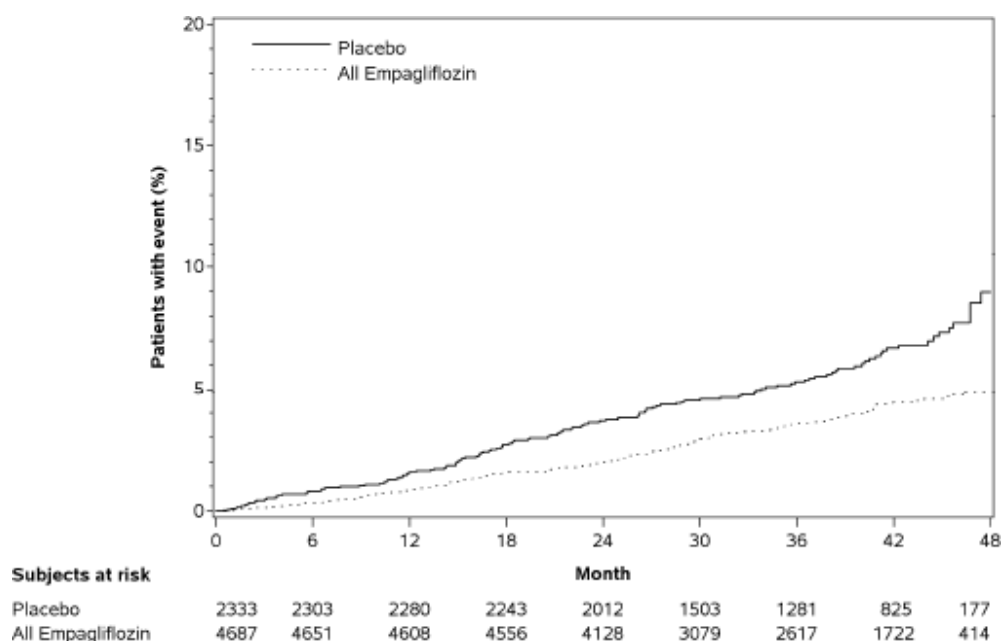
The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths, and were balanced between the treatment groups (2.1% in patients treated with empagliflozin, and 2.4% of patients treated with placebo).

5.2. Pharmacokinetic properties:

Empagliflozin and metformin hydrochloride extended-release tablets

Administration of empagliflozin and metformin hydrochloride extended-release tablets with food resulted in no change in overall exposure of empagliflozin. For metformin hydrochloride 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 Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and Cmax were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 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. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

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

Metabolism

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

glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

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. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Metformin hydrochloride

<u>Absorption</u>

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin hydrochloride extended-release after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher Cmax of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin hydrochloride extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and Cmax. 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 Tmax by approximately 3 hours but Cmax was not affected.

<u>Distribution</u>

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, 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 hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin hydrochloride, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

<u>Metabolism</u>

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

<u>Elimination</u>

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

Empagliflozin and metformin hydrochloride extended-release tablets: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin hydrochloride extended-release tablets in renally impaired patients have not been performed (see sections 4.3 and 4.4).

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. 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 hydrochloride: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see sections 4.3 and 4.4).

Hepatic Impairment

Empagliflozin and metformin hydrochloride extended-release tablets: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin hydrochloride extended-release tablets in hepatically impaired patients have not been performed (see section 4.4).

Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and Cmax

increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

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

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

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin (see section 5.1).

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

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

Geriatric

Empagliflozin and metformin hydrochloride extended-release tablets: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of empagliflozin and metformin hydrochloride extended-release tablets in geriatric patients have not been performed (see sections 4.4 and 5.1).

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis (see section 5.1).

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

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of empagliflozin and metformin hydrochloride extended-release tablets in pediatric patients have not been performed.

Drug Interactions

Pharmacokinetic drug interaction studies with empagliflozin and metformin hydrochloride extended-release tablets have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin hydrochloride.
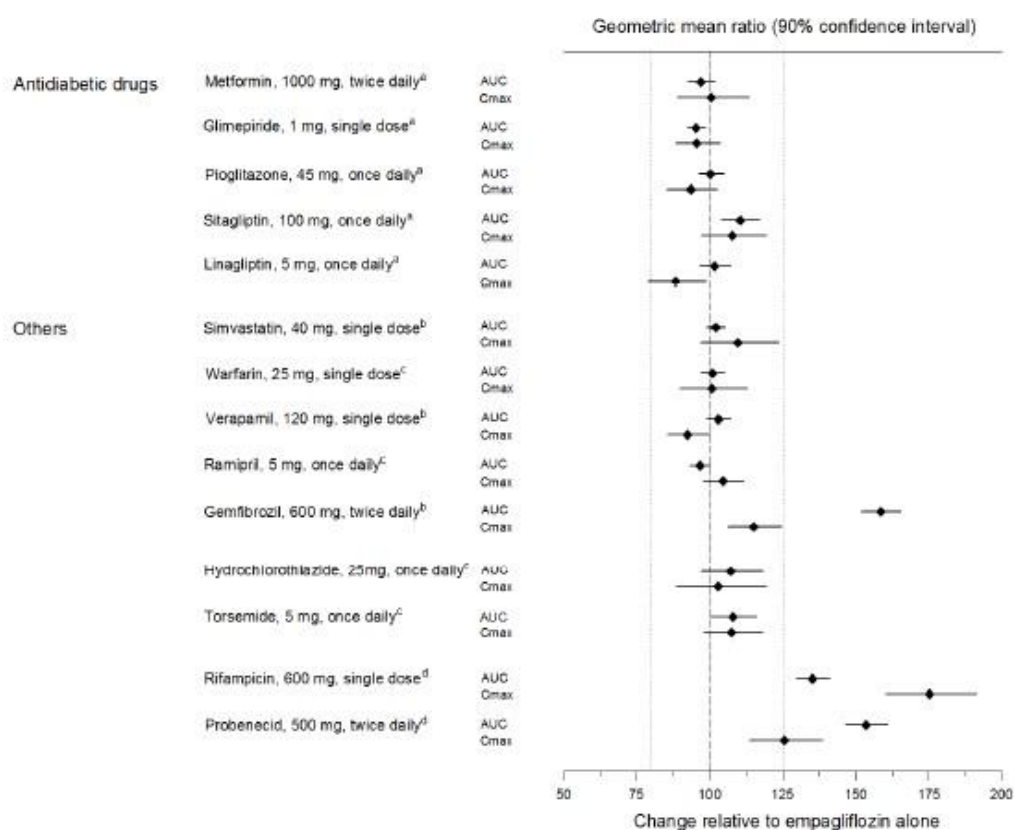
<u>Empagliflozin</u>

In vitro Assessment of Drug Interactions: Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho- glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions: No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin hydrochloride, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 4). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

Figure 4 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric

Mean AUC and Cmax Ratios [reference lines indicate 100% (80% - 125%)]

Geometric mean ratio (90% confidence interval)

Antidiabetic drugs	Metformin, 1000 mg, twice daily[a]	AUC Cmax
	Glimepiride, 1 mg, single dose[a]	AUC Cmax
	Pioglitazone, 45 mg, once daily[a]	AUC Cmax
	Sitagliptin, 100 mg, once daily[a]	AUC Cmax
	Linagliptin, 5 mg, once daily[d]	AUC Cmax
Others	Simvastatin, 40 mg, single dose[b]	AUC Cmax
	Warfarin, 25 mg, single dose[c]	AUC Cmax
	Verapamil, 120 mg, single dose[b]	AUC Cmax
	Ramipril, 5 mg, once daily[c]	AUC Cmax
	Gemfibrozil, 600 mg, twice daily[b]	AUC Cmax
	Hydrochlorothiazide, 25mg, once daily[c]	AUC Cmax
	Torsemide, 5 mg, once daily[c]	AUC Cmax
	Rifampicin, 600 mg, single dose[d]	AUC Cmax
	Probenecid, 500 mg, twice daily[d]	AUC Cmax

50   75   100   125   150   175   200
Change relative to empagliflozin alone

[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered with empagliflozin (see Figure 5).

Figure 5 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and Cmax Ratios [reference lines indicate 100% (80% - 125%)]

Geometric mean ratio (90% confidence interval)
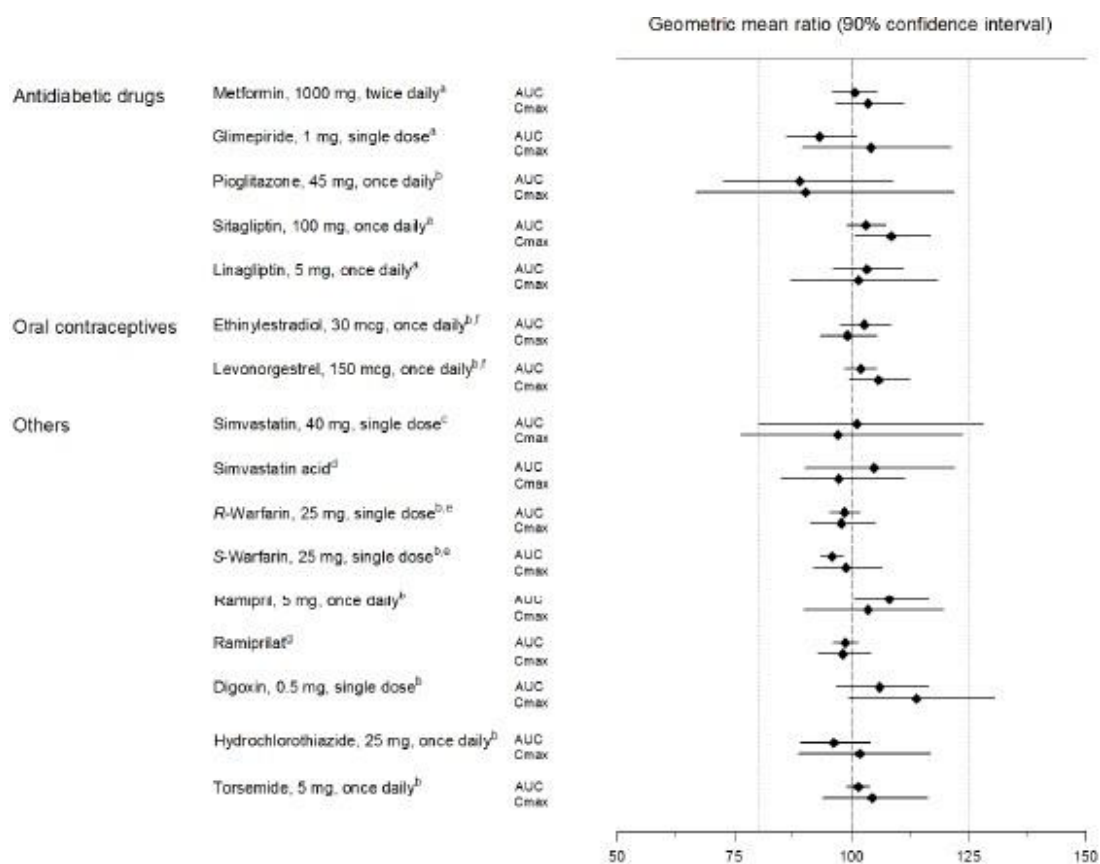
[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

Metformin hydrochloride

Table 10 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	Cmax
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg≠	metformin	0.98‡	0.99‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin (see sections 4.4 and 4.5).					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis (see sections 4.4 and 4.5).					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF)

≠ Metformin hydrochloride extended-release tablets 500 mg

‡ Ratio of arithmetic means

**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 11 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC†	Cmax
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF) unless otherwise noted

§ AUC(0-24 hr) reported

‡ Ratio of arithmetic means, p-value of difference <0.05

¶ Ratio of arithmetic means

5.3. Preclinical safety data:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Empagliflozin and metformin hydrochloride extended-release tablets

No animal studies have been conducted with the combination of empagliflozin and metformin hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility. 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

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 1000 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 1000 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.

Mutagenesis

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.

Impairment of Fertility

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 hydrochloride

Carcinogenesis

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 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 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.

Mutagenesis

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.

Impairment of Fertility

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.

6. Pharmaceutical particulars:
6.1. List of excipients

Empagliflozin and metformin hydrochloride extended-release tablets 10 mg/1000 mg

Hydroxy propyl methylcellulose
Polyethylene oxide
Magnesium stearate
Polyethylene glycol
Opadry II complete film coating system 47A180001 white
Opadry QX quick and flexible film coating system
321A540010 pink
Purified water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Empagliflozin and metformin hydrochloride extended-release tablets 10 mg/1000 mg

1) 30's Count:75 cc round white HDPE container with blue child resistant closure having induction seal.
2) 90's Count:250 cc round white HDPE container with white child resistant closure having induction seal.

6.6. Instructions for use, handling and disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Cipla Limited

8. Marketing authorization number

CTD9398

9. Date of first authorization/renewal of the authorization

29 June 2023

10. Date of revision of the text

11 May 2025