For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

COSPIAQ M

WARNING: LACTIC ACIDOSIS

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.
- Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.
- If metformin-associated lactic acidosis is suspected, immediately discontinue COSPIAQ M and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name

Empagliflozin and Metformin Hydrochloride (Extended Release) Tablets 12.5mg+1000mg, 25mg+1000mg

2. Qualitative and quantitative Composition:

COSPIAQ M (12.5 + 1000)

Each film coated bilayered tablet contains

Empagliflozin…….. 12.5 mg

Metformin Hydrochloride I.P. … 1000 mg

(As Extended Release)

Colour : Sunset Yellow FCF

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Polyvinyl Pyrrolidone, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicone Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Methylene Chloride, Triacetin, Sunset Yellow FCF.

COSPIAQ M (25 + 1000)

Each film coated bilayered tablet contains

Empagliflozin…….. 25 mg

Metformin Hydrochloride I.P. … 1000 mg

(As Extended Release)

Colour : Ferric Oxide (Yellow) USP-NF

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Polyvinyl Pyrrolidone, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicone Dioxide, Magnesium Stearate, Methylene Chloride, Hydroxy Propyl Methyl Cellulose, Triacetin, Ferric Oxide Yellow.

3. Dosage form and strength

Dosage form: Film coated bilayered tablet

Strength: 12.5mg+1000mg, 25mg+1000mg

4. Clinical particulars

4.1. Therapeutic indication

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

4.2. Posology and method of administration

Posology

Testing Prior to Initiation of COSPIAQ M

- Assess renal function before initiating COSPIAQ M and as clinically indicated.
- Assess volume status. In patients with volume depletion, correct this condition before initiating COSPIAQ M

Recommended Dosage and Administration of COSPIAQ M in Adults

- When switching to COSPIAQ M from:
  - Metformin HCl: initiate COSPIAQ M at a similar total daily dosage of metformin HCl and a total daily empagliflozin dosage of 10 mg.
  - Empagliflozin: initiate COSPIAQ M at the same total daily dosage of empagliflozin and a total daily metformin HCl dosage of 1,000 mg.
  - Empagliflozin and metformin HCl: initiate COSPIAQ M at the same total daily dosages of each component.
- Recommended dosage of COSPIAQ M :
  - The recommended total daily dosage of empagliflozin is 10 mg.
  - For additional glycemic control, empagliflozin may be increased to a maximum total daily dosage of 25 mg in patients tolerating 10 mg daily and metformin may be increased to a maximum total daily dosage of 2,000 mg, with gradual escalation to reduce gastrointestinal adverse reactions with metformin.

- Take COSPIAQ M orally once daily with a meal in the morning. Swallow each tablet whole. Do not split, crush, dissolve, or chew.

Dosage Recommendations in Patients with Renal Impairment

- Initiation of COSPIAQ M is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.
- COSPIAQ M are contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 or in patients on dialysis.

Discontinuation for Iodinated Contrast Imaging Procedures

- Discontinue COSPIAQ M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 COSPIAQ M if renal function is stable.

Temporary Interruption for Surgery

Withhold COSPIAQ M for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume COSPIAQ M when the patient is clinically stable and has resumed oral intake.

Recommendations Regarding Missed Dose

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

Method of administration

Take COSPIAQ M orally once daily with a meal in the morning. Swallow each tablet whole. Do not split, crush, dissolve, or chew.

4.3. Contraindications

COSPIAQ M are contraindicated in patients with:

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- Hypersensitivity to empagliflozin, metformin or any of the excipients in COSPIAQ M , reactions such as angioedema have occurred.

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 COSPIAQ M . In COSPIAQ M -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 COSPIAQ M 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:

- Before initiating COSPIAQ M , obtain an estimated glomerular filtration rate (eGFR).
- COSPIAQ M are contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking COSPIAQ M . 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 COSPIAQ M with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop COSPIAQ M at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 COSPIAQ M 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. COSPIAQ M 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 COSPIAQ M .

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 COSPIAQ M .

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 COSPIAQ M in patients with clinical or laboratory evidence of hepatic disease.

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, empagliflozin, a component of COSPIAQ M , significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose co-transporter 2 (SGLT2) inhibitors compared to patients who received placebo and fatal ketoacidosis has occurred with empagliflozin. COSPIAQ M are not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including COSPIAQ M .

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing COSPIAQ M ; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue COSPIAQ M , promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting COSPIAQ M .

Withhold COSPIAQ M , if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume COSPIAQ M when the patient is clinically stable and has resumed oral intake.

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue COSPIAQ M and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating COSPIAQ M in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating COSPIAQ M . Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

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

Hypoglycemia

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

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

Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier’s gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including

empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with COSPIAQ M presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue COSPIAQ M , closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

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

Lower Limb Amputation

In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95% CI) (0.81, 1.36).

In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg treatment arms, respectively. Amputation of the toe and mid-foot were most frequent (21 out of 28 empagliflozin 10 mg treated patients with lower limb amputations), and some involving above and below the knee. Some patients had multiple amputations. COSPIAQ M are not indicated for the treatment of chronic kidney disease.

Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot, peripheral artery disease (including previous amputation) or diabetes.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving COSPIAQ M for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

Hypersensitivity Reactions

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

Vitamin B12 Deficiency

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

4.5. Drugs interactions

Table 1 for clinically relevant interactions with COSPIAQ M .

Table 1 Clinically Relevant Interactions with COSPIAQ M XR

Carbonic Anhydrase Inhibitors	
Clinical Impact	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 COSPIAQ M may increase the risk of lactic acidosis.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism
Intervention	Warn patients against excessive alcohol intake while receiving COSPIAQ M .
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating COSPIAQ M , assess volume status and renal function. In patients with volume depletion, correct this condition before initiating COSPIAQ M . Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	

Clinical Impact	The risk of hypoglycemia is increased when COSPIAQ M is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of COSPIAQ M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving COSPIAQ M , the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving COSPIAQ M , the patient should be observed closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during COSPIAQ M initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.

Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from empagliflozin, COSPIAQ M are not recommended during the second and third trimesters of pregnancy.

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

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

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

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Metformin HCl: Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2,000 mg, based on body surface area (mg/m2) for rats and rabbits, respectively.

Empagliflozin and Metformin HCl: No adverse developmental effects were observed when empagliflozin and metformin HCl were co-administered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2,000 mg dose.

Lactation

Risk Summary

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

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of COSPIAQ M is not recommended while breastfeeding.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Females and Males of Reproductive Potential

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

Pediatric Use

Safety and effectiveness of COSPIAQ M have not been established in pediatric patients.

Geriatric Use

Assess renal function more frequently in COSPIAQ M -treated geriatric patients because there is a greater risk of empagliflozin-associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients.

The recommended dosage for the metformin component of COSPIAQ M in geriatric patients should usually start at the lower end of the dosage range.

Empagliflozin

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

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

safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients.

Metformin

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

Renal Impairment

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

Empagliflozin

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

Metformin

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

Hepatic Impairment

Use of metformin HCl in patients with hepatic impairment has been associated with some cases of lactic acidosis. COSPIAQ M are not recommended in patients with hepatic impairment.

4.7. Effects on ability to drive and use machines

There is no data available of influence on the ability to drive and use machines.

4.8. Undesirable effects

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

- Lactic Acidosis
- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis
- Volume Depletion
- Urosepsis and Pyelonephritis
- Hypoglycemia
- Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)
- Genital Mycotic Infections
- Lower Limb Amputation
- Hypersensitivity Reactions
- Vitamin B_{12} Deficiency

Clinical Trials Experience

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

The safety of concomitantly administered empagliflozin (daily dosage 10 mg or 25 mg) and metformin HCl (mean daily dosage of approximately 1,800 mg) has been evaluated in 3,456 adult patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1,271 patients received a daily dosage of empagliflozin 10 mg, and 1,259 patients received a daily dosage of empagliflozin 25 mg.

Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

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

In a 24-week placebo-controlled trial of empagliflozin 10 mg or 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported in ≥5% of empagliflozin-treated patients and more commonly than in placebo-treated patients are presented in Table 2 (see also Table 1).

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

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

Empagliflozin

Clinical Trials in Adults with Type 2 Diabetes Mellitus

The data in Table 3 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin in adult patients with type 2 diabetes mellitus. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials. These data reflect exposure of 1,976 adult patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes mellitus more than 5 years and had

a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes mellitus 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 3 shows adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in empagliflozin-treated patients than placebo-treated patients, and occurred in greater than or equal to 2% of empagliflozin-treated patients.

Table 3 Adverse Reactions Reported in ≥2% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of Empagliflozin Monotherapy or Combination Therapy

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

[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 in adults, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction.

Increased Urination

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

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

The incidence of hypoglycemia in adults by trial is shown in Table 4. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

Table 4 Incidence of Overall[a] and Severeb Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**Empagliflozin 10 mg (n=224)**	**Empagliflozin 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0

In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[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 dosage of trial drug)

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

Other Adverse Reactions in Clinical Trials with Empagliflozin in Adults

- *Genital Mycotic Infections*: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 mg or 25 mg.

  Genital mycotic infections occurred more frequently in female than male patients (see Table 3).

  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 3). 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
- Lower Limb Amputations: Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95% CI) (0.81, 1.36). In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg

treatment arms, respectively. COSPIAQ M are not indicated for the treatment of chronic kidney disease.

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

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

Adverse Reactions with Clinical Trials of Metformin

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

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

Pediatric Patients

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

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin or Metformin

Empagliflozin

- *Increases in Serum Creatinine and Decreases in eGFR:* Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of adults with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.
- *Increase in Low-Density Lipoprotein Cholesterol (LDL-C):* Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in adults treated with

empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

- *Increase in Hematocrit:* In a pool of four placebo-controlled trials in adults, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Metformin

- *Decrease in Vitamin B_{12}:* In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.

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

Gastrointestinal Disorders: Constipation

Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis

Metabolism and Nutrition Disorders: Ketoacidosis

Renal and Urinary Disorders: Acute kidney injury

Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin HCl

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

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Removal of empagliflozin by hemodialysis has not been studied.

5. Pharmacological properties

5.1. Mechanism of Action

COSPIAQ M contain: empagliflozin, a SGLT2 inhibitor, and metformin, a biguanide.

Empagliflozin

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

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

Metformin HCl

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

5.2. Pharmacodynamic properties

Empagliflozin

Urinary Glucose Excretion

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

Urinary Volume

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

Cardiac Electrophysiology

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

5.3. Pharmacokinetic properties

COSPIAQ M

Administration of COSPIAQ M with food resulted in no change in overall exposure of empagliflozin. For metformin HCl extended-release high-fat meals increased systemic exposure to metformin (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.

Empagliflozin

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steady- state mean plasma AUC and Cmax were 1,870 nmol□h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 nmol.h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once- daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Absorption

The absolute bioavailability of a metformin HCl 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Metformin HCl extended-release

Following a single oral dose of 1,000 mg (2 x 500 mg tablets) metformin HCl extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1,000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin HCl extended-release from 500 mg to 2,500 mg resulted in less than proportional increase in both AUC and C_{max}. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

Geriatric Patients

COSPIAQ M : Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of COSPIAQ M in geriatric patients have not been performed.

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

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

Pediatric Patients

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

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

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

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

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

Patients with Renal Impairment

COSPIAQ M : Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of COSPIAQ M in renally impaired patients have not been performed.

Empagliflozin: In adult patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 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 patients on dialysis due to kidney failure, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

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

Patients with Hepatic Impairment

COSPIAQ M : Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of COSPIAQ M in hepatically impaired patients have not been performed.

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

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

Drug Interaction Studies

Pharmacokinetic drug interaction studies with COSPIAQ M have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin HCl.

Empagliflozin

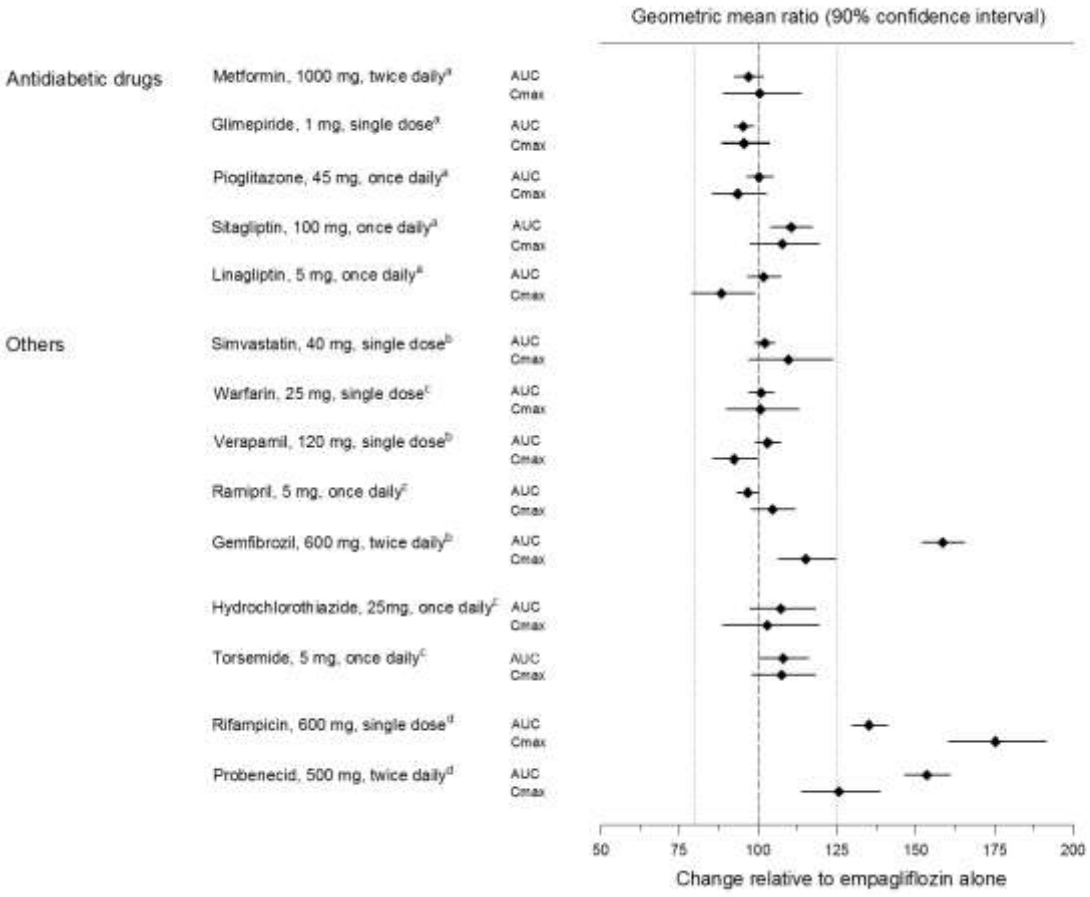
In vitro Assessment of Drug Interactions: Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and 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: Empagliflozin pharmacokinetics were similar with and without coadministration of metformin HCl, 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 mellitus (see Figure 1). 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 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]

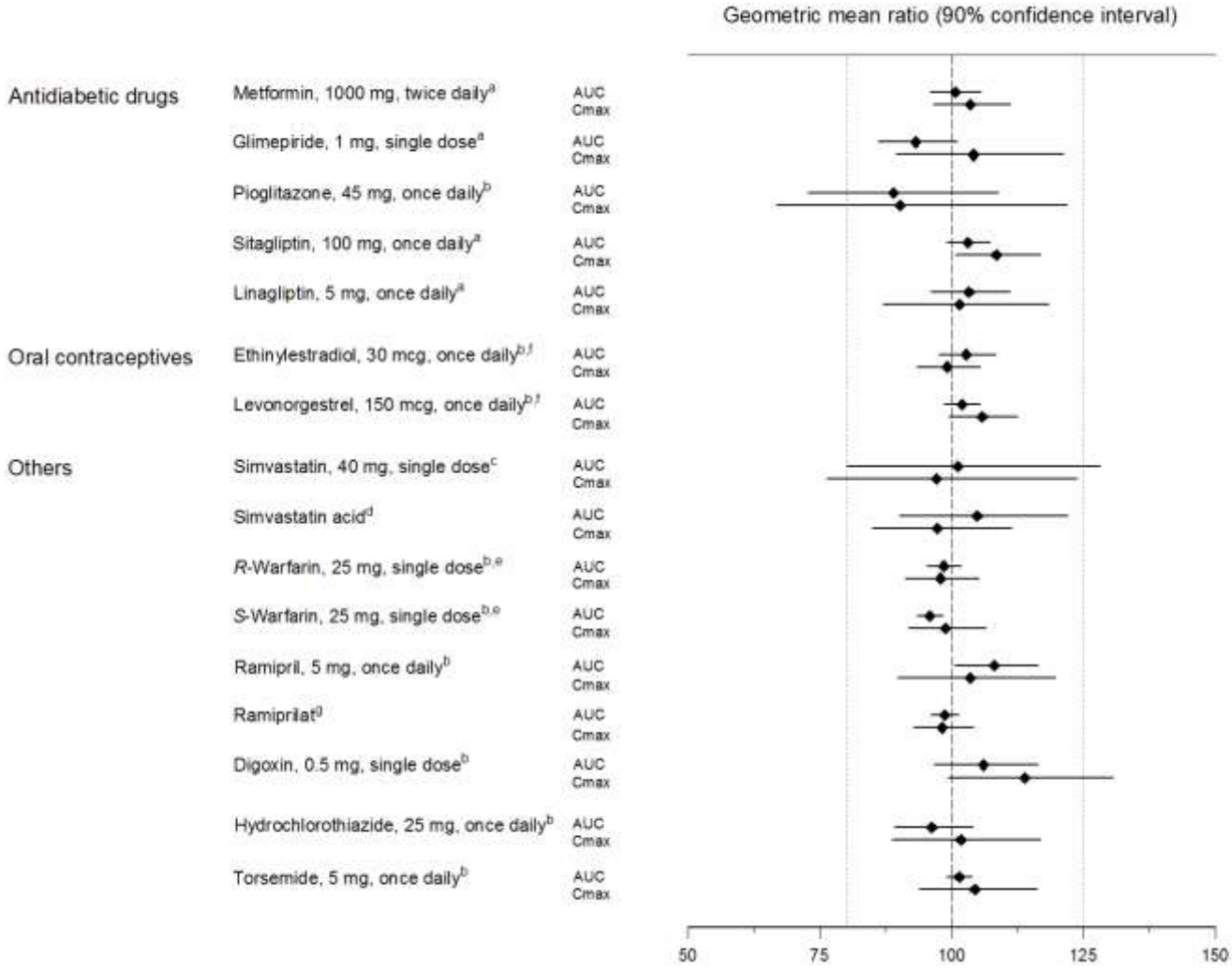


[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

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 in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various

Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[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 HCl

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	Cmax
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‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination .					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis .					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF)

≠ Metformin HCl 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 = AUC(0-12 hours)

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin)No effect=1.0		
				AUC†	Cmax
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
‡ Ratio of arithmetic means, p-value of difference <0.05
§ AUC(0-24 hours) reported
¶ Ratio of arithmetic means

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

COSPIAQ M

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

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

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

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

Metformin HCl

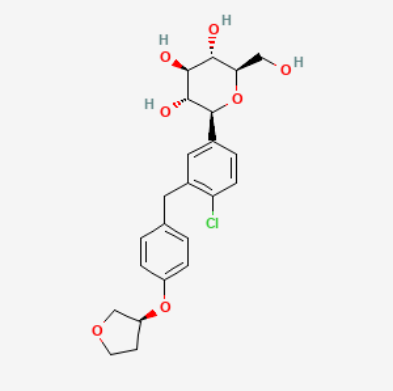
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000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

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

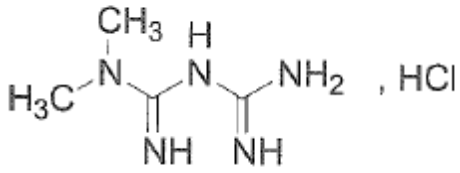
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

7. Description

.Empagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol. The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.9 g/mol. The chemical structure of Empagliflozin is:



Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula is $C_4H_{11}N_5$, HCl and its molecular weight is 165.6 g/mol. The chemical structure of Metformin Hydrochloride is:



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COSPIAQ M (12.5 + 1000)

Empagliflozin and Metformin Hydrochloride (Extended Release) Tablets are one layer light orange coloured and other layer white to off white coloured, elongated, biconvex plain on both sides, film coated bilayered tablets.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Polyvinyl Pyrrolidone, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicone Dioxide, Magnesium Stearate, Methylene Chloride, Hydroxy Propyl Methyl Cellulose, Triacetin, Sunset Yellow FCF.

COSPIAQ M (25 +1000)

Empagliflozin and Metformin Hydrochloride (Extended Release) Tablets are one layer light yellow coloured and other layer white coloured, oval shape, biconvex plain on both sides, film coated bilayered tablets.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Sodium Starch Glycolate, Polyvinyl Pyrrolidone, Isopropyl alcohol, Croscarmellose Sodium, Colloidal Silicone Dioxide, Magnesium Stearate, Methylene Chloride, Hydroxy Propyl Methyl Cellulose, Triacetin, Ferric Oxide Yellow..

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

COSPIAQ M is available in blister pack of 10 tablets.

8.4. Storage and handing instructions

Store below 30°C.

Keep all the medicine out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems

- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

M/s. Pure & Cure Healthcare Pvt. Ltd.

(A Subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot No.-26A, 27-30, Sector-8A, I.I.E.,

SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand

11. Details of permission or licence number with date

31/UA/2013 issued on 19.12.2024

12. Date of revision

NA

MARKETED BY

Torrent Pharmaceuticals Ltd.

IN/COSPIAQ M (12.5mg+1000mg) & (25mg+1000mg)/FEB-2025/01/PI