

**EMPAZIO M 12.5+500**

**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.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information.

If metformin-associated lactic acidosis is suspected, immediately discontinue EMPAZIO M and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

**1. Generic Name**

Empagliflozin and Metformin Hydrochloride Tablets 12.5 mg + 500 mg

**2. Qualitative and quantitative Composition:**

**Empagliflozin and Metformin Hydrochloride Tablets 12.5 mg + 500 mg**

Each film coated tablet contains:

Empagliflozin.....12.5 mg

Metformin Hydrochloride I.P. ....500 mg

Excipients.....q.s.

Colours: Titanium Dioxide I.P. and Black oxide of Iron and Red oxide of Iron

The excipients are Copovidone, Corn starch, Colloidal silicon dioxide, Magnesium stearate, Opadry Pink 02B240004, Microcrystalline cellulose, Povidone K-30, MCC PH 101 (Flocel 101).

**3. Dosage form and strength**

**Dosage form:** Film coated tablet.

**Strength:** 12.5 mg + 500 mg

**4. Clinical particulars**

**4.1. Therapeutic indication**

It is indicated as an adjunct to diet and exercise to improve glycemic 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*

#### **Prior to Initiation of EMPAZIO M**

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

#### **Recommended Dosage and Administration**

- Individualize the starting dose of EMPAZIO M based on the patient's current regimen:
  - In patients on metformin hydrochloride (HCl), switch to EMPAZIO M containing empagliflozin 5 mg with a similar total daily dose of metformin HCl;
  - In patients on empagliflozin, switch to EMPAZIO M containing metformin HCl 500 mg with a similar total daily dose of empagliflozin;
  - In patients already treated with empagliflozin and metformin HCl, switch to **EMPAZIO M** containing the same total daily doses of each component.
- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg and metformin HCl 2000 mg.
- Take **EMPAZIO M** twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

#### **Dosage Recommendations in Patients with Renal Impairment**

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

#### **Discontinuation for Iodinated Contrast Imaging Procedures**

Discontinue EMPAZIO 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<sup>2</sup>; 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 EMPAZIO M if renal function is stable.

### *Method of administration*

- Oral use
- The tablet should be swallowed whole and never crushed, cut, or chewed.

## 4.3. Contraindications

- Severe renal impairment (eGFR below 30 mL/min/1.73 m<sup>2</sup>), end stage renal disease, or on dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- Hypersensitivity to empagliflozin, metformin or any of the formulation excipients in this FDC product.

#### 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 EMPAZIO M. In EMPAZIO 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 EMPAZIO 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 EMPAZIO M, obtain an estimated glomerular filtration rate (eGFR).
- EMPAZIO M is contraindicated in patients with an eGFR below 30 mL/min/1.73 m<sup>2</sup>.
- Obtain an eGFR at least annually in all patients taking EMPAZIO 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 EMPAZIO 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 EMPAZIO 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<sup>2</sup>; 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 EMPAZIO 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. EMPAZIO 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 EMPAZIO 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 EMPAZIO 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 EMPAZIO M in patients with clinical or laboratory evidence of hepatic disease.

### **Ketoacidosis**

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and 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. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. EMPAZIO M is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with EMPAZIO M 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 EMPAZIO M may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, EMPAZIO M should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the post marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating EMPAZIO M, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing EMPAZIO M for at least 3 days prior to surgery.

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

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue EMPAZIO 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 post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m<sup>2</sup>), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating EMPAZIO 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 EMPAZIO M. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy

### **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.

### **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues**

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. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with EMPAZIO M.

### **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 postmarketing surveillance 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 EMPAZIO 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

EMPAZIO 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.

### 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 EMPAZIO M; treat promptly per standard of care, and monitor until signs and symptoms resolve. EMPAZIO M is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in EMPAZIO M.

### Vitamin B12 Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B<sub>12</sub> 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 EMPAZIO M and manage any abnormalities.

## 4.5. Drugs interactions

**Table: Clinically Relevant Interactions with EMPAZIO M**

<b>Carbonic Anhydrase Inhibitors</b>	
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.
Intervention	Concomitant use of these drugs with EMPAZIO M may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
<b>Drugs that Reduce Metformin Clearance</b>	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis
Intervention	Consider the benefits and risks of concomitant use.
<b>Alcohol</b>	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving EMPAZIO M.

<b>Diuretics</b>	
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 EMPAZIO M, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating EMPAZIO M. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
<b>Insulin or Insulin Secretagogues</b>	
Clinical Impact	The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue.
Intervention	Coadministration of EMPAZIO M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
<b>Drugs Affecting Glycemic Control</b>	
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 EMPAZIO M, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving EMPAZIO M, the patient should be observed closely for hypoglycemia.
<b>Positive Urine Glucose Test</b>	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

**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, EMPAZIO M is not recommended during the second and third trimesters of pregnancy.

The limited available data with EMPAZIO 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 EMPAZIO 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 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<sup>2</sup>) 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 limited information regarding the presence of EMPAZIO 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 EMPAZIO 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 EMPAZIO M have not been established in pediatric patients.

### **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.

#### *Empagliflozin*

In empagliflozin type 2 diabetes studies, 2721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these studies, 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.

#### *Metformin hydrochloride*

Clinical studies of metformin did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger adult patients.

### **Renal Impairment**

EMPAZIO M should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m<sup>2</sup> due to the metformin component and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m<sup>2</sup>), end stage renal disease, or dialysis.

#### *Empagliflozin*

The glucose lowering benefit of empagliflozin 25 mg decreased in 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.

#### *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.

### **Hepatic Impairment**

Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. EMPAZIO M is not recommended in patients with hepatic impairment.

#### **4.7. Effects on ability to drive and use machines**

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

#### **4.8. Undesirable effects**

The following important adverse reactions are described below:

- Lactic Acidosis
- Ketoacidosis
- Volume Depletion
- Urosepsis and Pyelonephritis

- Hypoglycemia with Concomitant Use with Insulin and Insulin
- Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)
- Genital Mycotic Infections
- Hypersensitivity Reactions
- Vitamin B<sub>12</sub> 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 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  $\geq 5\%$  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  $\geq 5\%$  of patients and more commonly than in patients given placebo are presented in Table 1

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

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*

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

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 m<sup>2</sup>).

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: 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**

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

<sup>a</sup>Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

<sup>b</sup>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).

<sup>c</sup>Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

<sup>d</sup>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.

#### 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. 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

The incidence of hypoglycemia by study is shown in shown table.

**Table; Incidence of Overall<sup>a</sup> and Severe<sup>b</sup> Hypoglycemic Events in Placebo-Controlled Clinical Studies<sup>c</sup>**

<b>Monotherapy (24 weeks)</b>	<b>Placebo (n=229)</b>	<b>Empagliflozin 10 mg (n=224)</b>	<b>Empagliflozin 25 mg (n=223)</b>
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
<b>In Combination with Metformin (24 weeks)</b>	<b>Placebo + Metformin (n=206)</b>	<b>Empagliflozin 10 mg + Metformin (n=217)</b>	<b>Empagliflozin 25 mg + Metformin (n=214)</b>
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
<b>In Combination with Metformin + Sulfonylurea (24 weeks)</b>	<b>Placebo (n=225)</b>	<b>Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)</b>	<b>Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)</b>
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
<b>In Combination with Pioglitazone +/- Metformin (24 weeks)</b>	<b>Placebo (n=165)</b>	<b>Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)</b>	<b>Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)</b>
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
<b>In Combination with Basal Insulin +/- Metformin (18 weeksd)</b>	<b>Placebo (n=170)</b>	<b>Empagliflozin 10 mg (n=169)</b>	<b>Empagliflozin 25 mg (n=155)</b>
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
<b>In Combination with MDI Insulin +/-Metformin</b>	<b>Placebo (n=188)</b>	<b>Empagliflozin 10 mg (n=186)</b>	<b>Empagliflozin 25 mg (n=189)</b>

<b>(18 weeksd)</b>			
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

<sup>a</sup>Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

<sup>b</sup>Severe hypoglycemic events: requiring assistance regardless of blood glucose

<sup>c</sup>Treated set (patients who had received at least one dose of study drug)

<sup>d</sup>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.

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 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%.

### *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.

### Laboratory Tests

#### *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 study of patients 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<sup>2</sup>, 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 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. 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*

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

#### **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 hydrochloride*

- 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](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**

Empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), and metformin hydrochloride, 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 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 actually decrease.

### **5.2. Pharmacodynamic properties**

#### *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. 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

#### EMPAZIO M

Administration of 12.5 mg empagliflozin/1000 mg metformin hydrochloride under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C<sub>max</sub> for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C<sub>max</sub> decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant.

#### *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 C<sub>max</sub> 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.

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<sub>max</sub> 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 [<sup>14</sup>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. 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.

##### 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 [<sup>14</sup>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 hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 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<sub>max</sub>, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (T<sub>max</sub>) 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.

### Distribution

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. 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

#### Renal Impairment

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

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m<sup>2</sup>), moderate (eGFR: 30 to less than 60 mL/min/1.73 m<sup>2</sup>), and severe (eGFR: less than 30 mL/min/1.73 m<sup>2</sup>) renal impairment and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and kidney failure/ESRD 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 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.

### Hepatic Impairment

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

Empagliflozin: In 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<sub>max</sub> 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.

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 HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

### Geriatric

EMPAZIO M: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of EMPAZIO 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 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 C<sub>max</sub> 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.

### Drug Interactions

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

### *Empagliflozin*

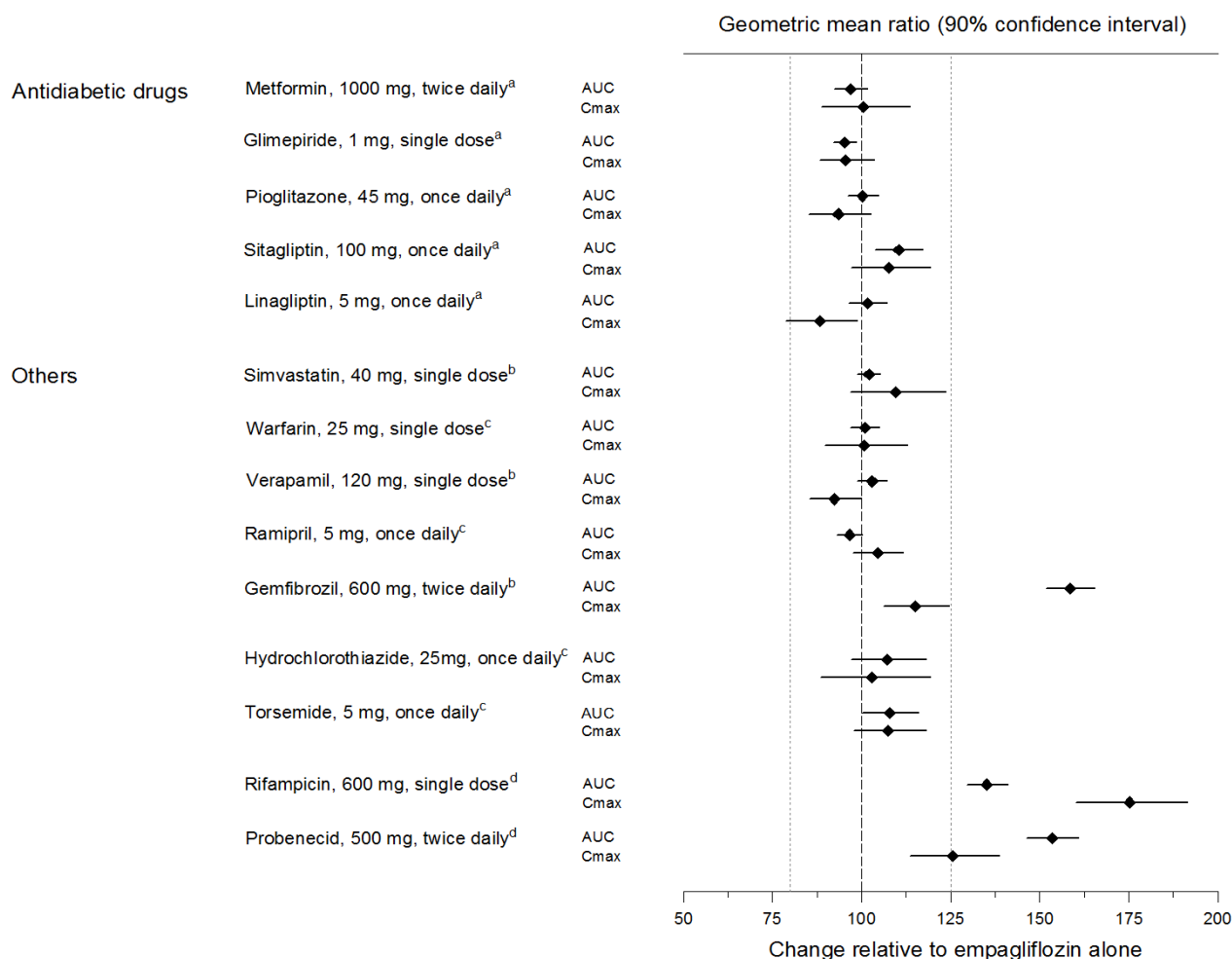
In vitro Assessment of Drug Interactions: Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. 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 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. 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.

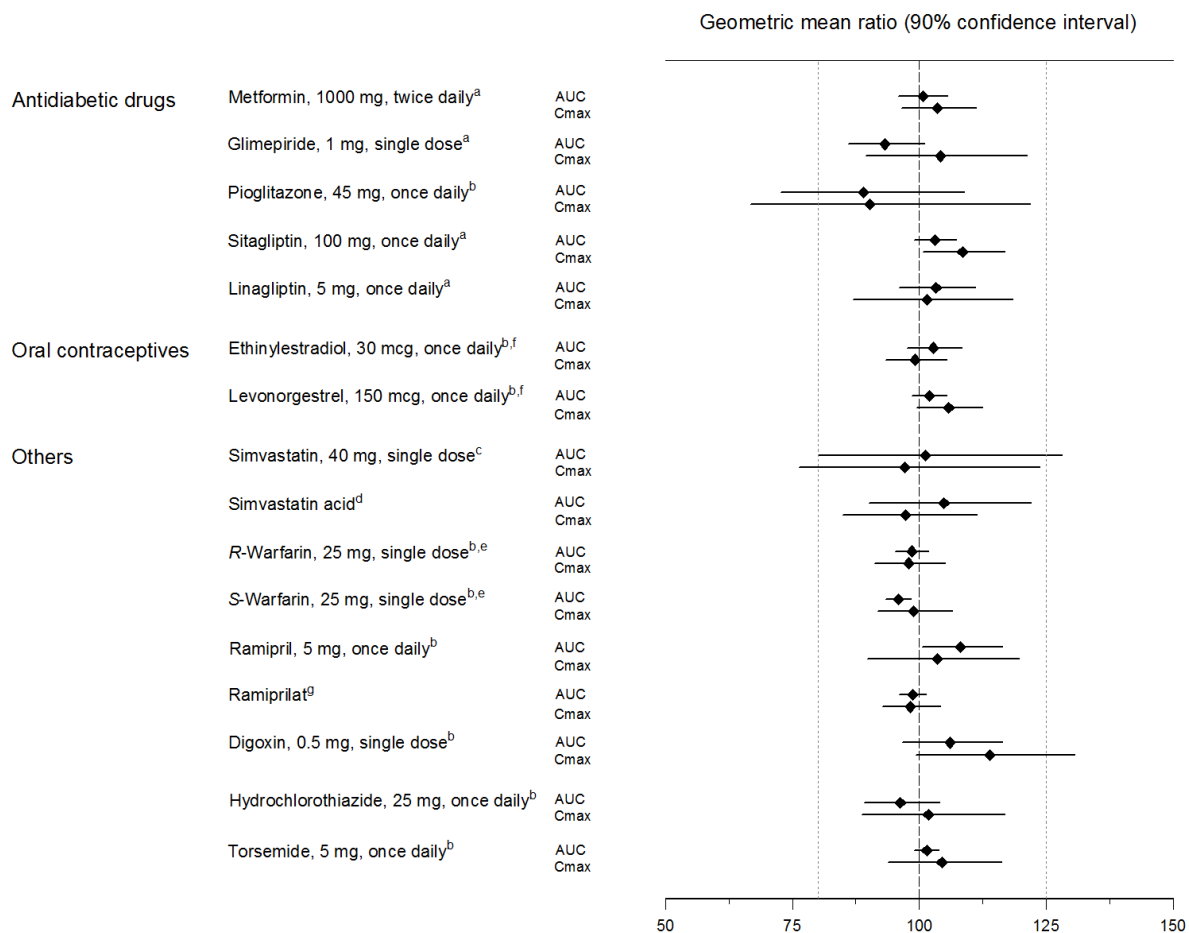
**Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C<sub>max</sub> Ratios [reference lines indicate 100% (80% - 125%)]**



<sup>a</sup>empagliflozin, 50 mg, once daily; <sup>b</sup>empagliflozin, 25 mg, single dose; <sup>c</sup>empagliflozin, 25 mg, once daily; <sup>d</sup>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

**Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C<sub>max</sub> Ratios [reference lines indicate 100% (80% - 125%)]**



<sup>a</sup>empagliflozin, 50 mg, once daily; <sup>b</sup>empagliflozin, 25 mg, once daily; <sup>c</sup>empagliflozin, 25 mg, single dose; <sup>d</sup>administered as simvastatin; <sup>e</sup>administered as warfarin racemic mixture; <sup>f</sup>administered as Microgynon®; <sup>g</sup>administered as ramipril

### Metformin hydrochloride

**Table: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure**

Coadministered Drug		Dose of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0	
AUC†			C <sub>max</sub>		
Glyburide	5 mg	850 mg	metformin	0.91‡	0.93‡
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‡
<b>Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination</b>					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
<b>Carbonic anhydrase inhibitors may cause metabolic acidosis</b>					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

\* All metformin and coadministered drugs were given as single doses

† AUC = AUC(INF)

‡ Ratio of arithmetic means

\*\*At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC(0-12hours)

**Table: Effect of Metformin on Coadministered Drug Systemic Exposure**

Coadministered Drug		Dose of Coadministered Drug*		Dose of Metformin hydrochloride*		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

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 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas 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 hydrochloride*

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.

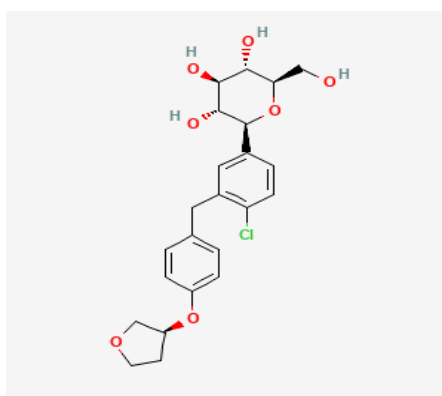
There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

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

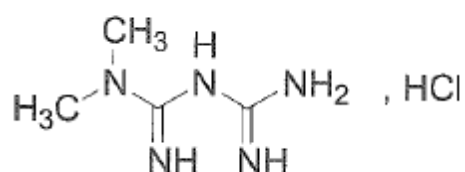
### Empagliflozin

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

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:



### EMPAZIO M 12.5+500

Pale brownish purple, oval shaped, biconvex, film-coated tablet debossed with “500” on one side and “12” on other side.



The excipients are Copovidone, Corn starch, Colloidal silicon dioxide, Magnesium stearate, Opadry Pink 02B240004, Microcrystalline cellulose, Povidone K-30, MCC PH 101 (Flocel 101).

## **8. Pharmaceutical particulars**

### **8.1. Incompatibilities**

Not applicable

### **8.2. Shelf-life**

Do not use later than the date of expiry.

### **8.3. Packaging information**

EMPAZIO M 12.5+500 is available in Blister strips of 10 Tablets each.

### **8.4. Storage and handing instructions**

Store at a temperature not exceeding 30°C.

Dose: As Directed by the Physician.

Keep 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**

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim - 737135

## **11. Details of permission or licence number with date**

Mfg Lic No.: M/563/2010 issued on 21/10/2024

## **12. Date of revision**

NA

### **MARKETED BY**



Torrent Pharmaceuticals Limited.

**IN/EMPAZIO M 12.5+500 mg/FEB-2025/01/PI**