

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

LINAXA EM

WARNING: LACTIC ACIDOSIS

Post marketing 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 LINAXA EM and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name

Empagliflozin, Linagliptin and Metformin Hydrochloride ER Tablets.

2. Qualitative and quantitative Composition:

LINAXA EM 10/5/1000

Each film coated tablet contains :

Empagliflozin10 mg

Linagliptin5 mg

Metformin Hydrochloride I.P.1000 mg

(As Extended Release)

Excipientsq.s.

Colour: Ferric Oxide USP-NF (Red)

The excipients used are Microcrystalline Cellulose, Meglumine, Mannitol, Crospovidone, Hydroxypropyl Cellulose, Croscarmellose Sodium, Colloidal Silicone Dioxide, Sodium Stearyl Fumarate, Dibasic Calcium Phosphate, Hydroxy Propyl Methyl Cellulose, Polyvinylpyrrolidone, carbomer homopolymer, Talcum, Magnesium Stearate, Triacetin, Methylene Chloride, Isopropyl Alcohol, Colour Ferric Oxide Red.

LINAXA EM 25/5/1000

Each film coated tablet contains :

Empagliflozin 25 mg
Linagliptin 5 mg
Metformin Hydrochloride I.P. 1000 mg

(As Extended Release)

Excipients q.s.

Colour: Ferric Oxide USP-NF (Yellow)

The excipients used are Microcrystalline Cellulose, Meglumine, Mannitol, Crospovidone, Hydroxypropyl Cellulose, Croscarmellose Sodium, Colloidal Silicone Dioxide, Sodium Stearyl Fumarate, Dibasic Calcium Phosphate, Hydroxy Propyl Methyl Cellulose, Polyvinylpyrrolidone, carbomer homopolymer, Talcum, Magnesium Stearate, Triacetin, Methylene Chloride, Isopropyl Alcohol, Colour Ferric Oxide Yellow.

3. Dosage form and strength

Dosage form: film coated tablet.

Strength: Empagliflozin, Linagliptin and Metformin (10 mg+5 mg +1000 mg) (25 mg+5 mg+1000 mg)

4. Clinical particulars

4.1 Therapeutic indication

It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

4.2 Posology and method of administration

Posology

Testing Prior to Initiation of LINAXA EM

- Assess renal function before initiating LINAXA EM and as clinically indicated.
- Assess volume status. In patients with volume depletion, correct this condition before initiating LINAXA EM Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of ferric carboxymaltose.

Recommended Dosage and Administration

- Individualize the starting dosage of LINAXA EM based on the patient's current regimen:
 - In patients on metformin HCl, with or without linagliptin, switch to LINAXA EM containing a similar total daily dosage of metformin HCl and a total daily dosage of empagliflozin 10 mg and linagliptin 5 mg;
 - In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to LINAXA EM containing a similar total daily dosage of metformin HCl, the same total daily dosage of empagliflozin and linagliptin 5 mg.

- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dosage of empagliflozin 25 mg, linagliptin 5 mg and metformin HCl 2,000 mg.
- Take LINAXA EM orally, once daily with a meal in the morning.

Take LINAXA EM 10 mg/5 mg/1,000 mg or LINAXA EM 25 mg/5 mg/1,000 mg as a single tablet once daily.

Patients with Renal Impairment

- Initiation of LINAXA EM is not recommended in patients with an eGFR less than 45 mL/min/1.73 m², due to the metformin component.

LINAXA EM is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² or in patients on dialysis.

Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue LINAXA EM at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart LINAXA EM if renal function is stable.

Temporary Interruption for Surgery

Withhold LINAXA EM for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume LINAXA EM 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

Swallow LINAXA EM tablets whole. Do not split, crush, dissolve, or chew.

4.3 Contraindications

LINAXA EM is contraindicated in patients with:

- severe renal impairment (eGFR less than 30 mL/min/1.73 m²), end-stage renal disease, or dialysis
- acute or chronic metabolic acidosis, including diabetic ketoacidosis hypersensitivity to empagliflozin, linagliptin, metformin or any of the excipients in LINAXA EM.

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 LINAXA EM. In LINAXA EM-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 LINAXA EM 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 LINAXA EM, obtain an estimated glomerular filtration rate (eGFR).
- LINAXA EM is contraindicated in patients with an eGFR below 30 mL/min/1.73 m²
- Obtain an eGFR at least annually in all patients taking LINAXA EM. 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 LINAXA EM 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 LINAXA EM at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart LINAXA EM 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.

LINAXA EM 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 LINAXA EM.

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 LINAXA EM.

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 LINAXA EM 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 LINAXA EM, 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. LINAXA EM is 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 empagliflozin.

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 LINAXA EM; 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 LINAXA EM, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting.

LINAXA EM.

Withhold LINAXA EM, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume LINAXA EM when the patient is clinically stable and has resumed oral intake [see *Dosage and Administration (4.2)*].

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

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue LINAXA EM and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using LINAXA EM.

Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine [see *Adverse Reactions (6.1)*]. 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 LINAXA EM 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 LINAXA EM. 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 with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when LINAXA EM is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Therefore, a lower dosage of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with LINAXA EM.

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 LINAXA EM 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 LINAXA EM, 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. LINAXA EM is 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 LINAXA EM 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 in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with LINAXA EM.

There have been postmarketing reports of serious hypersensitivity reactions (e.g., angioedema) in patients treated with empagliflozin.

If a hypersensitivity reaction occurs, discontinue LINAXA EM, treat promptly per standard of care, and monitor until signs and symptoms resolve. LINAXA EM is contraindicated in patients with hypersensitivity to linagliptin, empagliflozin or any of the excipients in LINAXA EM.

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 LINAXA EM and manage any abnormalities.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking linagliptin. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving LINAXA EM. If bullous pemphigoid is suspected, LINAXA EM should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of LINAXA EM prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of LINAXA EM.

4.5 Drugs interactions

Table 1: Clinically Relevant Interactions with LINAXA EM

Carbonic Anhydrase Inhibitors	
<i>Clinical Impact</i>	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 LINAXA EM may increase the risk of lactic acidosis.

<i>Intervention</i>	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
<i>Clinical Impact</i>	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.
<i>Intervention</i>	Consider the benefits and risks of concomitant use.
Alcohol	
<i>Clinical Impact</i>	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
<i>Intervention</i>	Warn patients against excessive alcohol intake while receiving LINAXA EM.
Diuretics	
<i>Clinical Impact</i>	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
<i>Intervention</i>	Before initiating LINAXA EM, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating LINAXA EM. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
<i>Clinical Impact</i>	The risk of hypoglycemia is increased when LINAXA EM is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin.
<i>Intervention</i>	Coadministration of LINAXA EM 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	
<i>Clinical Impact</i>	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.
<i>Intervention</i>	When such drugs are administered to a patient receiving LINAXA EM, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving LINAXA EM, the patient should be observed closely for hypoglycemia.
Lithium	
<i>Clinical Impact</i>	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
<i>Intervention</i>	Monitor serum lithium concentration more frequently during LINAXA EM initiation and dosage changes.
Inducers of P-glycoprotein or CYP3A4 Enzymes	

<i>Clinical Impact</i>	Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.
<i>Intervention</i>	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.
Positive Urine Glucose Test	
<i>Clinical Impact</i>	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
<i>Intervention</i>	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	
<i>Clinical Impact</i>	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
<i>Intervention</i>	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, LINAXA EM is not recommended during the second and third trimesters of pregnancy.

The limited available data with LINAXA EM, linagliptin, 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 LINAXA EM, 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 linagliptin or metformin were 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).

Linagliptin: No adverse developmental outcome was observed when linagliptin was administered to pregnant

Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1,943-times (rabbits) the 5 mg maximum clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

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.

Lactation

Risk Summary

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

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of LINAXA EM 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 LINAXA EM have not been established in pediatric patients.

Geriatric Use

Assess renal function more frequently in LINAXA EM-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 LINAXA EM in geriatric patients should usually start at the lower end of the dosage range.

Of the 273 patients treated with the combination of empagliflozin, linagliptin, and metformin hydrochloride to improve glycemic control in adults with type 2 diabetes mellitus, 58 were 65 years of age and older, while 8 were 75 years of age and older.

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.

Linagliptin

In linagliptin trials, 1,085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin trials, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

Metformin

Clinical trials 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

LINAXA EM 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 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

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. LINAXA EM is 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

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.

Empagliflozin, Linagliptin and Metformin

The safety of concomitantly administered empagliflozin (daily dosage 10 mg or 25 mg), linagliptin (daily dosage 5 mg) and metformin has been evaluated in a total of 686 patients with type 2 diabetes mellitus treated for up to 52 weeks in an active-controlled clinical trial. The most common adverse reactions are shown in Table 2.

Table 2: Adverse Reactions Reported in $\geq 5\%$ of Patients Treated with Empagliflozin, Linagliptin, and Metformin in an Active-Controlled Clinical Trial of 52 Weeks

Adverse Reactions	Empagliflozin 10 mg + Linagliptin 5 mg + Metformin (%) n=136	Empagliflozin 25 mg + Linagliptin 5 mg + Metformin (%) n=137
Upper respiratory tract infection	10.3	8.0
Urinary tract infection ^a	9.6	10.2
Nasopharyngitis	8.1	5.8
Diarrhea	6.6	2.2
Constipation	5.1	5.8
Headache	5.1	5.1
Gastroenteritis	2.9	5.8

^aPredefined grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Hypoglycemia

The incidence of hypoglycemia (defined as plasma or capillary glucose of less than 54 mg/dL) was 0.7% in patients receiving empagliflozin 10 mg/linagliptin 5 mg/metformin and 0.7% in patients receiving empagliflozin 25 mg/linagliptin 5 mg/metformin. Events of severe hypoglycemia (requiring assistance regardless of blood glucose) did not occur in this trial.

Empagliflozin Adverse reactions that occurred in $\geq 2\%$ of patients receiving empagliflozin and more commonly than in patients given placebo included (10 mg, 25 mg, and placebo): urinary tract infection (9.3%, 7.6%, and 7.6%), female genital mycotic infections (5.4%, 6.4%, and 1.5%), upper respiratory tract infection (3.1%, 4.0%, and 3.8%), increased urination (3.4%, 3.2%, and 1.0%), dyslipidemia (3.9%, 2.9%, and 3.4%), arthralgia (2.4%, 2.3%, and 2.2%), male genital mycotic infections (3.1%, 1.6%, and 0.4%), and nausea (2.3%, 1.1%, and 1.4%).

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

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Events related to volume depletion (hypotension and syncope) were reported in 3 patients (1.1%) treated with empagliflozin, linagliptin and metformin combination therapy.

Linagliptin

Adverse reactions reported in $\geq 2\%$ of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% and 6.1%), diarrhea (3.3% and 3.0%), and cough (2.1% and 1.4%).

Other adverse reactions reported in clinical trials with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient-year exposure while being treated with linagliptin, compared with 3.7 cases per 10,000 patient-year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Metformin

The most common (>5%) 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%).

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.

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. 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. LINAXA EM is not indicated for the treatment of chronic kidney disease.

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin, Linagliptin, 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 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

m², respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in 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: 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.

Linagliptin

Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the linagliptin group and

≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group).

Increase in Lipase: In a placebo-controlled clinical trial with linagliptin in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the linagliptin arm, compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the linagliptin and placebo arms, respectively.

Increase in Amylase: In a cardiovascular safety trial comparing linagliptin versus glimepiride in patients with type 2 diabetes mellitus, amylase levels above 3 times upper limit of normal were seen in 1.0% compared to 0.5% of patients in the linagliptin and glimepiride arms, respectively.

The clinical significance of elevations in lipase and amylase with linagliptin is unknown in the absence of other signs and symptoms of pancreatitis [see *Warnings and Precautions (4.4)*].

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.

6.2 Post marketing Experience

Additional adverse reactions have been identified during postapproval use of linagliptin, empagliflozin, or metformin. 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.

- *Gastrointestinal Disorders:* Acute pancreatitis, including fatal pancreatitis, mouth ulceration, stomatitis
- *Immune System Disorders:* Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- *Infections:* Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis

- *Metabolism and Nutrition Disorders:* Ketoacidosis
- *Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis, severe and disabling arthralgia.
- *Renal and Urinary Disorders:* Acute kidney injury
- *Skin and Subcutaneous Tissue Disorders:* Bullous pemphigoid, skin reactions (e.g., rash, urticaria) • *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/contact-us/customer-service/> 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, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

5 Pharmacological properties

5.1 Mechanism of Action

LINAXA EM

LINAXA EM contains: empagliflozin, a SGLT2 inhibitor, linagliptin, a DPP-4 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.

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

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. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 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 recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100 mg dose. At the 100 mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

5.3 Pharmacokinetic properties

LINAXA EM

Administration of LINAXA EM with food resulted in no change in overall exposure of empagliflozin or linagliptin. For metformin extended-release, high-fat meals increased systemic exposure (as measured by area under the curve [AUC]) by approximately 70% relative to fasting, while C_{max} is not affected. Meals prolonged T_{max} by approximately 3 hours.

Empagliflozin

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

Absorption

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

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population.

pharmacokinetic analysis. Following administration of an oral [¹⁴C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Elimination

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

Metabolism

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

Excretion

Following administration of an oral [¹⁴C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin

Absorption

The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1,110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Elimination

Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metabolism

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion

Following administration of an oral [14 C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Metformin HCl extended-release

Absorption

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

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

Geriatric Patients

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis [see *Use in Special Populations* (4.6)].

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.

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.

Linagliptin: Based on the population PK analysis, age, body mass index (BMI), gender and race do not have a clinically meaningful effect on pharmacokinetics of linagliptin.

Metformin HCl: 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 Whites (n=249), Blacks or African Americans (n=51), and Hispanics or Latinos (n=24).

Patients with Renal Impairment

LINAXA EM: Studies characterizing the pharmacokinetics of empagliflozin, linagliptin, and metformin after administration of LINAXA EM in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) renal impairment and patients on dialysis due to kidney failure, AUC of empagliflozin

increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment, as compared to 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.

Linagliptin: An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥ 80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%), compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Metformin HCl: 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

LINAXA EM: Studies characterizing the pharmacokinetics of empagliflozin, linagliptin, and metformin after administration of LINAXA EM 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_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max}

compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

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

Drug Interaction Studies

Pharmacokinetic drug interaction studies with LINAXA EM have not been performed; however, such studies have been conducted with the individual components of LINAXA EM (empagliflozin, linagliptin, 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'-diphosphoglucuronosyltransferases 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.

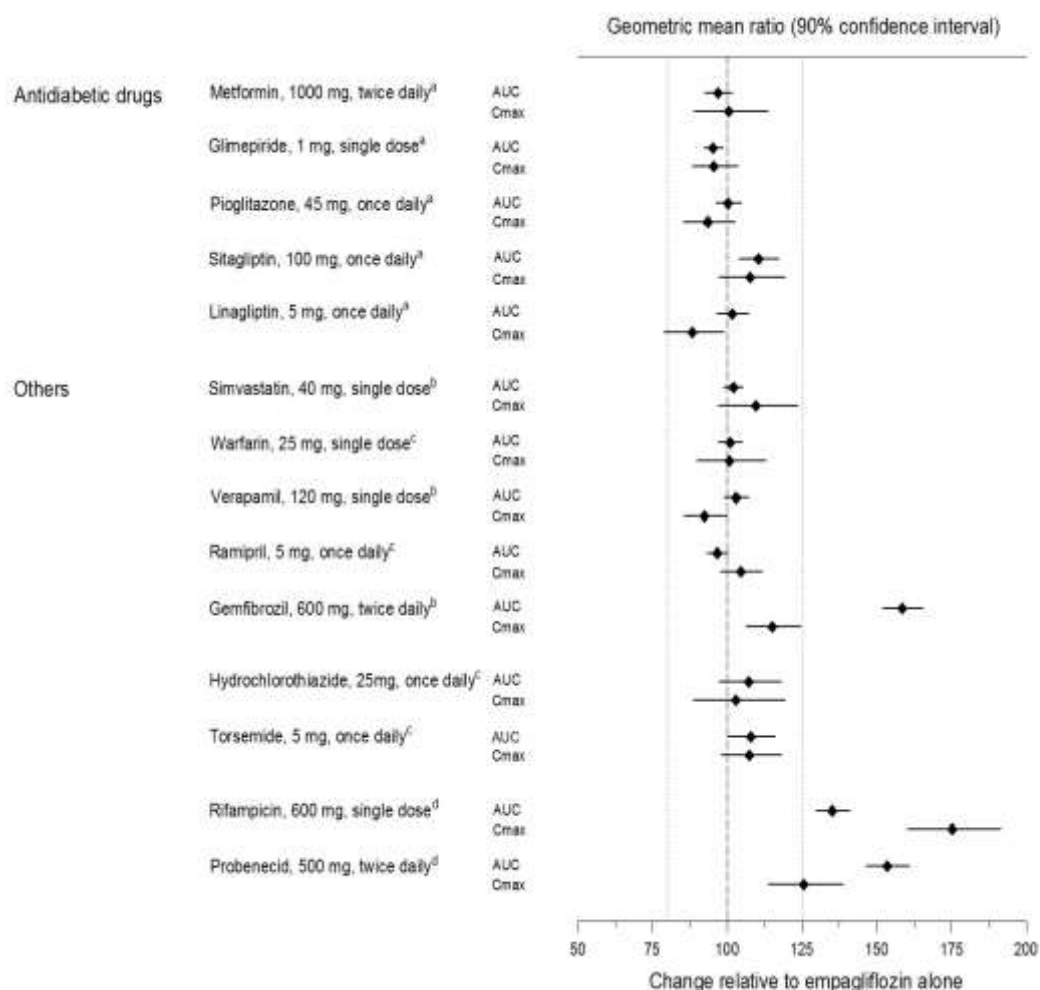
Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin 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, 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. 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.

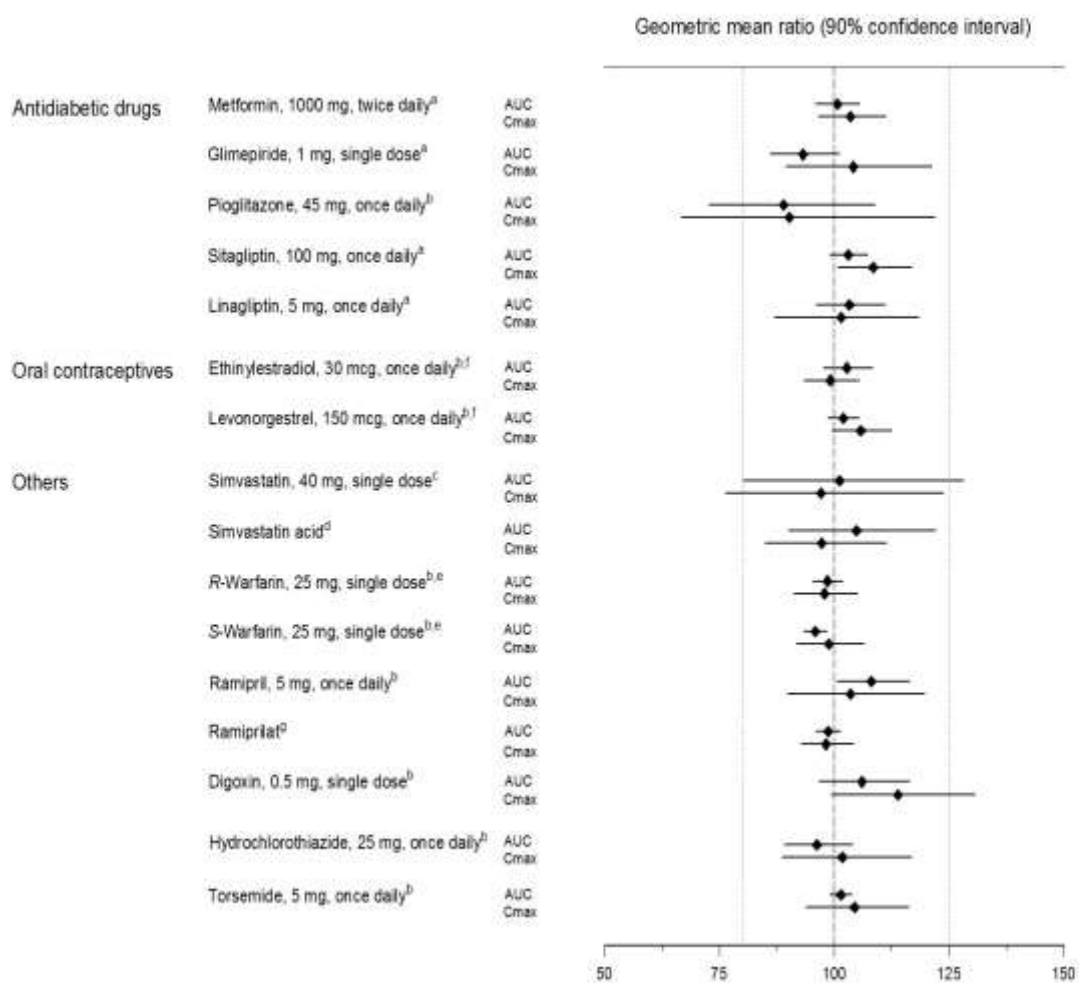
Figure 1: Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and Cmax Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, single dose; ^cempagliflozin, 25 mg, once daily; ^dempagliflozin, 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.

Figure 2: Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and Cmax Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, once daily; ^cempagliflozin, 25 mg, single dose; ^dadministered as simvastatin; ^eadministered as warfarin racemic mixture; ^fadministered as Microgynon[®]; ^gadministered as ramipril

Linagliptin

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4 but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results, and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations [see *Drug Interactions (4.5)*]. *In vivo*

studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 3: Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug ^a	Dosing of Linagliptin ^a	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0	
			AUC ^d	C _{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg ^c	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg ^c	2.01	2.96
Rifampin ^b	600 mg QD	5 mg QD	0.60	0.56

^aMultiple dose (steady-state) unless otherwise noted ^bFor information regarding clinical recommendations

^cSingle dose

^dAUC = AUC(0 to 24 hours) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments QD = once daily

BID = twice daily, TID = three times daily

Table 4: Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug ^a	Dosing of Linagliptin ^a	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC ^c	C _{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg ^b	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone	0.94	0.86
			metabolite M-III	0.98	0.96
			metabolite M-IV	1.04	1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin	1.34	1.10
			simvastatin acid	1.33	1.21
Warfarin	10 mg ^b	5 mg QD	R-warfarin	0.99	1.00
			S-warfarin	1.03	1.01
			INR	0.93 ^d	1.04 ^d
			PT	1.03 ^d	1.15 ^d
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol	1.01	1.08
			levonorgestrel	1.09	1.13

^aMultiple dose (steady-state) unless otherwise noted ^bSingle dose

^cAUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments

^dAUC = AUC(0-168) and C_{max} = E_{max} for pharmacodynamic end points

INR = International Normalized Ratio PT = Prothrombin Time

QD = once daily TID = three times daily

Metformin HCl

Table 5: Effect of Coadministered Drugs on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
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 [see Drug Interactions (4.5)].					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis [see Drug Interactions (4.5)].					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

*All metformin and coadministered drugs were given as single doses

[†]AUC = AUC(INF)

[≠]Metformin 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	Dosing of Coadministered Drug*	Dosing of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC [†]	C _{max}
Glyburide	5 mg	500 mg [§]	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10 [§]	1.08
Propranolol	40 mg	850 mg	propranolol	1.01 [§]	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95 [§]	1.01

*All metformin and coadministered drugs were given as single doses

[†]AUC = AUC(INF) unless otherwise noted

[§]AUC(0-24 hours) reported

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

[¶]Ratio of arithmetic means

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

LINAXA EM

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin, linagliptin, and metformin HCl.

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).

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35 and 270 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215 times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

Metformin HCl

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1,200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of 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 rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of

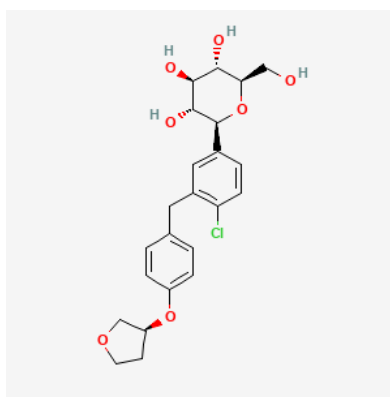
up to 2,000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative.

Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

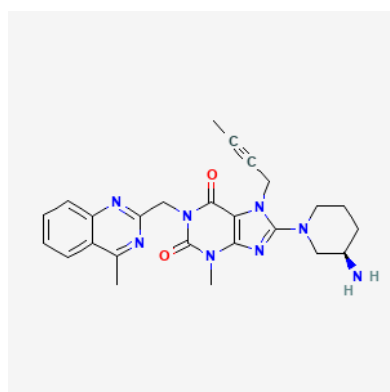
7 Description

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:

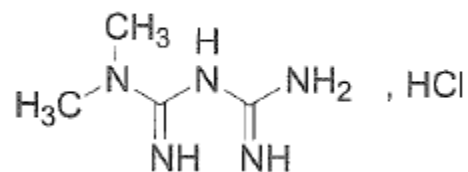


Linagliptin is 8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]purine-2,6-dione. The empirical formula is

$C_{25}H_{28}N_8O_2$ and its molecular weight is 472.5 g/mol. The chemical structure of Linagliptin 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:



LINAXA EM 10/5/1000

Empagliflozin, Linagliptin and Metformin Hydrochloride ER Tablets are one layer light red to red colored and other layer white to off white colored, oval shaped, biconvex plain on both sides, film coated tablets.

The excipients used are Microcrystalline Cellulose, Meglumine, Mannitol, Crospovidone, Hydroxypropyl Cellulose, Croscarmellose Sodium, Colloidal Silicone Dioxide, Sodium Stearyl Fumarate, Dibasic Calcium Phosphate, Hydroxy Propyl Methyl Cellulose, Polyvinylpyrrolidone, carbomer homopolymer, Talcum, Magnesium Stearate, Triacetin, Methylene Chloride, Isopropyl Alcohol, Colour Ferric Oxide Red.

LINAXA EM 25/5/1000

Empagliflozin, Linagliptin and Metformin Hydrochloride ER Tablets are one layer light yellow to yellow colored and other layer white to off white coloured, oval shape, biconvex plain on both sides, film coated bilayered tablets.

The excipients used are Microcrystalline Cellulose, Meglumine, Mannitol, Crospovidone, Hydroxypropyl Cellulose, Croscarmellose Sodium, Colloidal Silicone Dioxide, Sodium Stearyl Fumarate, Dibasic Calcium Phosphate, Hydroxy Propyl Methyl Cellulose, Polyvinylpyrrolidone, carbomer homopolymer, Talcum, Magnesium Stearate, Triacetin, Methylene Chloride, Isopropyl Alcohol, Colour 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

LINAXA EM 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.

Tablet should be swallowed whole and not to be chewed or crushed.

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

Mfg. Lic. No. 31/UA/2013 issued on 03.02.2025

12 Date of revision

NA

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/LINAXA EM (10 mg+5 mg +1000 mg) (25 mg+5 mg+1000 mg)/Mar-2025/01/PI