

SUMMARY OF PRODUCT CHARACTERISTICS(SPC)

1. NAME OF THE MEDICINAL PRODUCT

EMPAZOX-L 10/5 TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Empagliflozin.....10 mg

Linagliptin.....5 mg

Excipient of known effect:

Lactose Monohydrate

For full list of excipients. See section 6.1

3. PHARMACEUTICAL FORM

Tablets

Orange color, arc triangular shape, beveledged, film coated tablets, debossed with '51' on one side and 'V' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Empagliflozin and Linagliptin Tablets is a combination of empagliflozin and linagliptin 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.

Limitations of Use

Empagliflozin and Linagliptin Tablets is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Empagliflozin and Linagliptin Tablets has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using Empagliflozin and Linagliptin Tablets.

Empagliflozin and Linagliptin Tablets is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m². Empagliflozin and Linagliptin Tablets is likely to be ineffective in this setting based upon its mechanism of action.

4.2 Posology and method of administration

Prior to Initiation of Empagliflozin and Linagliptin Tablets

- Assess renal function before initiating Empagliflozin and Linagliptin Tablets and as clinically indicated

- In patients with volume depletion, correct this condition before initiating Empagliflozin and Linagliptin Tablets.

Recommended Dosage

The recommended dose of Empagliflozin and Linagliptin Tablets is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. Empagliflozin and Linagliptin Tablets dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily for additional glycemic control.

Dosage Recommendations in Patients with Renal Impairment

Empagliflozin and Linagliptin Tablets is not recommended for use in patients with an eGFR less than 30 mL/min/1.73 m² and contraindicated in patients on dialysis.

4.3 Contraindications

- Patients on dialysis
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in Empagliflozin and Linagliptin Tablets, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.

4.4 Special warnings and precautions for use

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 post marketing 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 Empagliflozin and Linagliptin Tablets 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 Empagliflozin and Linagliptin Tablets.

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. Empagliflozin and Linagliptin Tablets is not indicated for the treatment of patients with type 1 diabetes mellitus.

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

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

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

For patients who undergo scheduled surgery, consider temporarily discontinuing Empagliflozin and Linagliptin Tablets for at least 3 days prior to surgery.

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

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Empagliflozin and Linagliptin Tablets and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

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

Urosepsis and Pyelonephritis

There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving 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 and Linagliptin Tablets is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Empagliflozin and Linagliptin Tablets.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

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

Genital Mycotic Infections

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

Hypersensitivity Reactions

There have been 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 Empagliflozin and Linagliptin Tablets.

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

If a hypersensitivity reaction occurs, discontinue Empagliflozin and Linagliptin Tablets, treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin and Linagliptin Tablets is contraindicated in

patients with hypersensitivity to linagliptin, empagliflozin or any of the excipients in Empagliflozin and Linagliptin Tablets.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. 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 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 Empagliflozin and Linagliptin Tablets. If bullous pemphigoid is suspected, Empagliflozin and Linagliptin Tablets 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 Empagliflozin and Linagliptin Tablets 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 Empagliflozin and Linagliptin Tablets

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

Table 1 Clinically Relevant Interactions with Empagliflozin and Linagliptin Tablets

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 Empagliflozin and Linagliptin Tablets, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating Empagliflozin and Linagliptin Tablets. 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 Empagliflozin and Linagliptin Tablets is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin
<i>Intervention</i>	Coadministration of Empagliflozin and Linagliptin Tablets 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.
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 Empagliflozin and Linagliptin Tablets 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.
<i>Interference with 1,5-anhydroglucitol (1,5-AG) Assay</i>	
<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 Fertility, Pregnancy and Lactation:

Use In Specific Populations:

Pregnancy:

Risk Summary

Based on animal data showing adverse renal effects from empagliflozin, Empagliflozin and Linagliptin Tablets is not recommended during the second and third trimesters of pregnancy

The limited available data with Empagliflozin and Linagliptin Tablets, linagliptin, or empagliflozin in pregnant women are not sufficient to determine a drug-

associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

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

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

Animal Data

The combined components administered during the period of organogenesis were not teratogenic in rats up to and including a combined dose of 700 mg/kg/day empagliflozin and 140 mg/kg/day linagliptin, which is 253- and 353-times the clinical exposure. A pre- and postnatal development study was not conducted with the combined components of Empagliflozin and Linagliptin Tablets.

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 1943-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.

Lactation

Risk Summary

There is limited information regarding the presence of Empagliflozin and Linagliptin Tablets, or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Empagliflozin and linagliptin are present in rat milk. 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 GLYXAMBI is not recommended while breastfeeding.

Data

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.

Pediatric Use

Safety and effectiveness of Empagliflozin and Linagliptin Tablets have not been established in pediatric patients

Geriatric Use

Empagliflozin and Linagliptin Tablets

Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older

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.

Linagliptin

In linagliptin studies, 1085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients

Renal Impairment

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.

Efficacy and safety studies with empagliflozin did not enroll patients with ESRD on dialysis or

patients with an eGFR less than $30 \frac{\text{mL}}{\text{min}}/1.73 \text{ m}^2$. Empagliflozin is contraindicated in patients on dialysis.

Hepatic Impairment

Empagliflozin and Linagliptin Tablets may be used in patients with hepatic impairment.

4.7 Overdose:

In the event of an overdose with Empagliflozin and Linagliptin Tablets, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely

Description

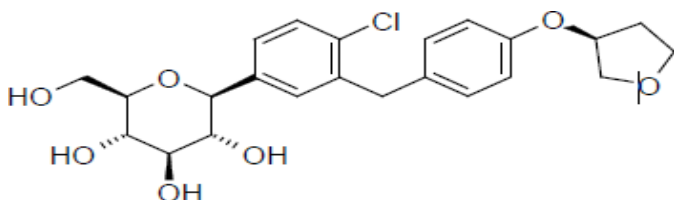
Empagliflozin and Linagliptin Tablets tablets for oral use contain: empagliflozin and linagliptin.

Empagliflozin

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3furanyl]oxy]phenyl] methyl]phenyl]-, (1S).

The molecular formula is C₂₃H₂₇ClO₇ and the molecular weight is 450.91. The structural formula is:



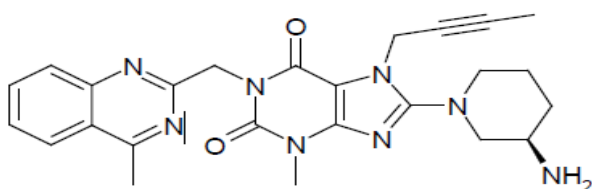
Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Linagliptin

Linagliptin is an inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

The molecular formula is C₂₅H₂₈N₈O₂ and the molecular weight is 472.54. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.

Empagliflozin and Linagliptin Tablets

Empagliflozin and Linagliptin Tablets are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin. The inactive ingredients of Empagliflozin and Linagliptin Tablets are the following: Tablet Core: mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc and magnesium stearate. Coating: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol and ferric oxide, yellow (10 mg/5 mg) or ferric oxide, red (25 mg/5 mg).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority via Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org/>

5. PHARMACOLOGICAL PROPERTIES:

5.1 Mechanism of Action

Empagliflozin and Linagliptin Tablets

Empagliflozin and Linagliptin Tablets contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor

Empagliflozin

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (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.

5.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. 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 Pharmacokinetics

Empagliflozin and Linagliptin Tablets

Administration of the fixed-dose combination with food resulted in no change in overall exposure of empagliflozin or linagliptin; however, the peak exposure was decreased 39% and 32% for empagliflozin and linagliptin, respectively. These changes are not likely to be clinically significant.

Absorption

Empagliflozin

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_{max} 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_{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.

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. 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

Empagliflozin

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

14

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%.

Linagliptin

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 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

Empagliflozin: 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.

Linagliptin: 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

Empagliflozin: 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.

Linagliptin: 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

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

Linagliptin: 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.

Specific Populations

Renal Impairment

Empagliflozin and Linagliptin Tablets: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of Empagliflozin and Linagliptin Tablets 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] $\geq$ 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 and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes 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_{t,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 and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes groups, renal excretion was below 7% of the administered dose.

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

Hepatic Impairment

Empagliflozin and Linagliptin Tablets: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of Empagliflozin and Linagliptin Tablets 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.

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.

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.

Drug Interactions

Pharmacokinetic drug interaction studies with Empagliflozin and Linagliptin Tablets have not been performed; however, such studies have been conducted with the individual components of

Empagliflozin and Linagliptin Tablets (empagliflozin and linagliptin).

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

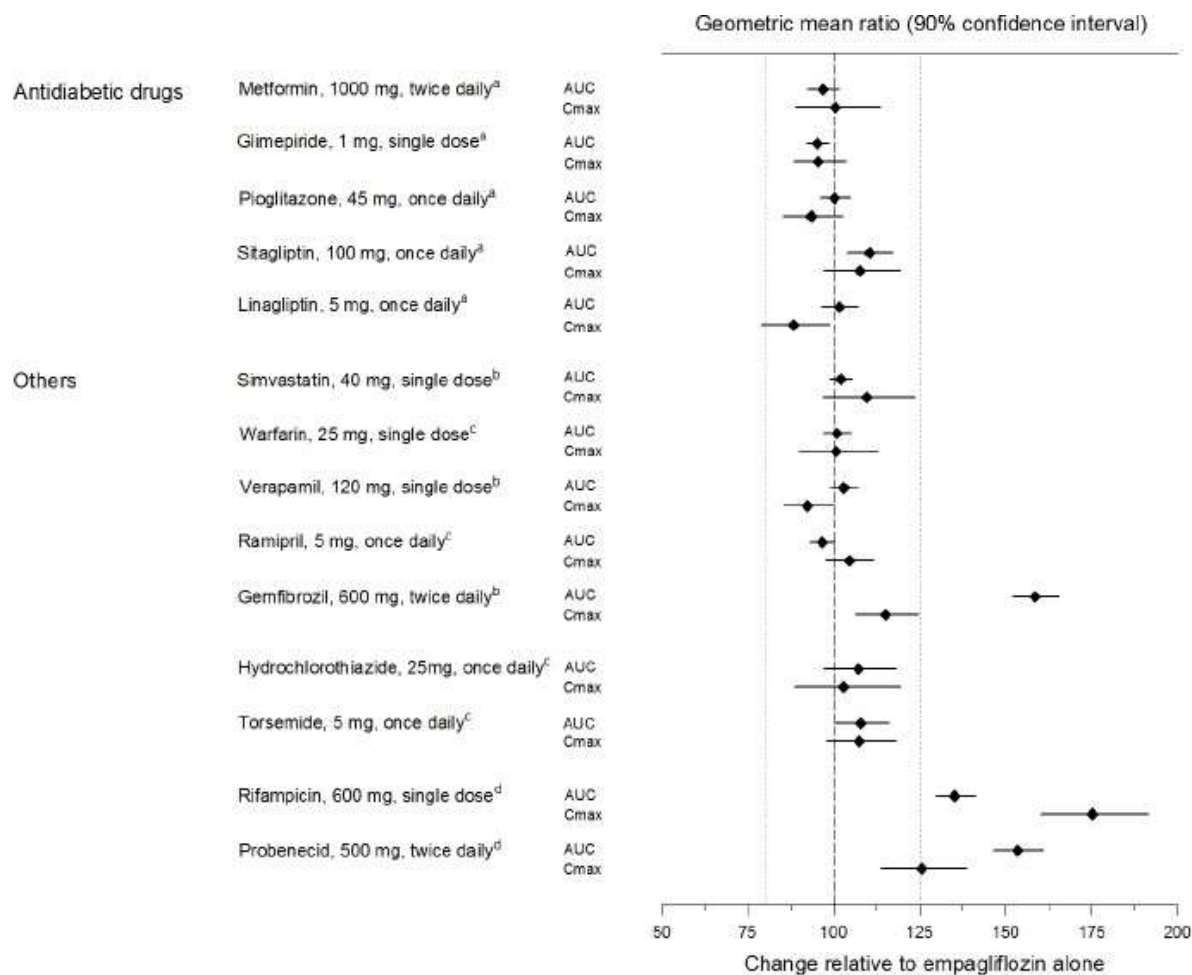
on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

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 (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

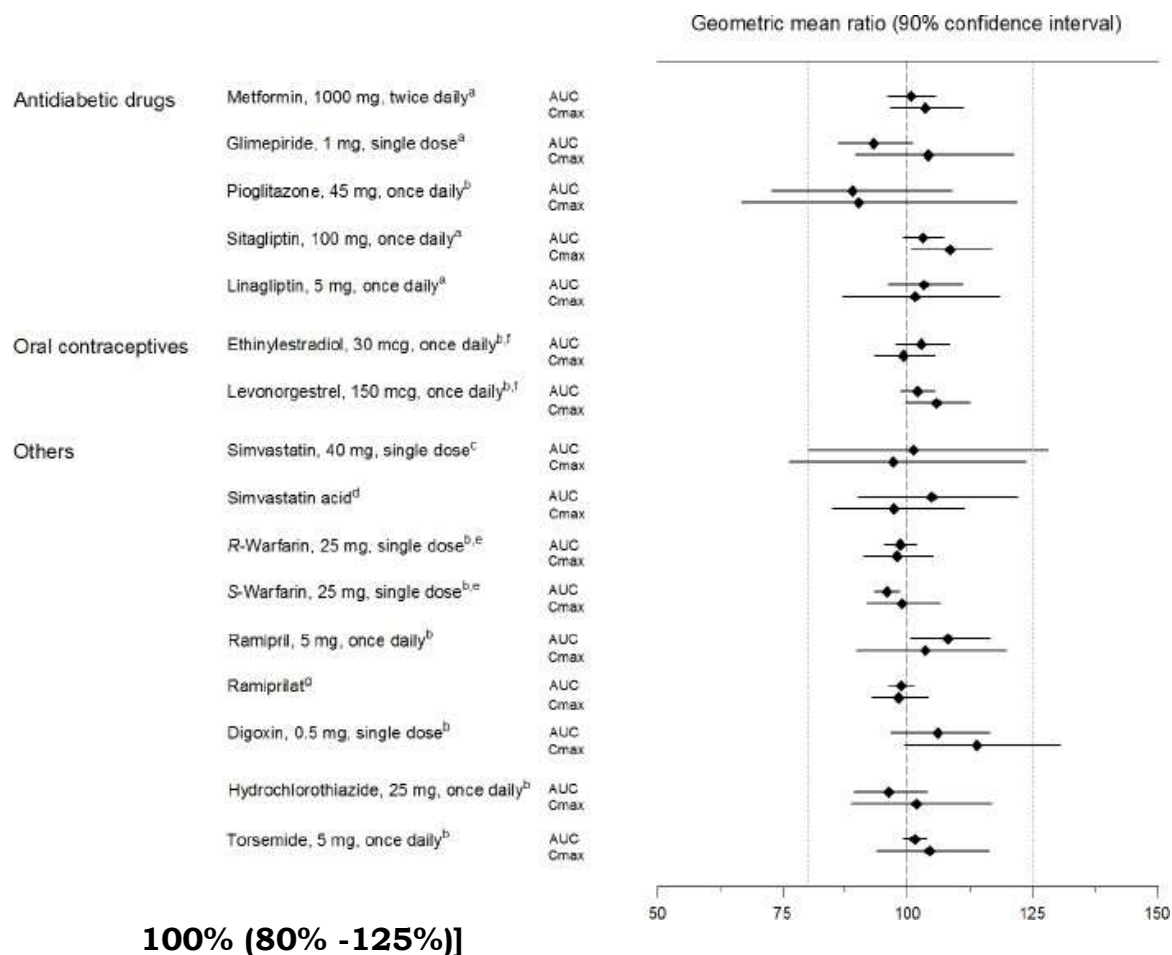
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and Cmax Ratios [reference lines indicate 100% (80% -125%)]



^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 (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and Cmax Ratios [reference lines indicate



^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. *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 2 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	200 mg BID	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 3 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 S-warfarin INR PT	0.99 1.03 0.93 ^d 1.03 ^d	1.00 1.01 1.04 ^d 1.15 ^d
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 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

Non Clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Empagliflozin and linagliptin

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

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 were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

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)

Clinical Studies:

Empagliflozin and linagliptin Tablets Glycemic Control Studies

Add-on Combination Therapy with Metformin

A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of empagliflozin 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg empagliflozin as a fixed dose combination tablet.

At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with Empagliflozin and linagliptin Tablets_25 mg/5 mg or Empagliflozin and linagliptin Tablets 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference compared to empagliflozin alone.

Table 4Glycemic Parameters at 24 Weeks in a Study Comparing Empagliflozin and linagliptin Tablets to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin and linagliptin Tablets 10 mg/5 mg	Empagliflozin and linagliptin Tablets 25 mg/5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	Linagliptin 5 mg
HbA1c (%)					
Number of patients	n=135	n=133	n=137	n=139	n=128
Baseline (mean)	8.0	7.9	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.1	-1.2	-0.7	-0.6	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI) ^a	-0.4 (-0.6, -0.2) ^d	-0.6 (-0.7, -0.4) ^d	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI) ^a	-0.4 (-0.6, -0.2) ^d	-0.5 (-0.7, -0.3) ^d	--	--	--
Patients [n (%)] achieving HbA1c <7% ^b	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
Number of patients	n=133	n=131	n=136	n=137	n=125
Baseline (mean)	157	155	162	160	156
Change from baseline (adjusted mean)	-33	-36	-21	-21	-13
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI) ^a	-12 (-18, -5) ^d	-15 (-22, -9) ^d	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI) ^a	-20 (-27, -13) ^d	-23 (-29, -16) ^d	--	--	--
Body Weight					
Number of patients	n=135	n=134	n=137	n=140	n=128
Baseline (mean) in kg	87	85	86	88	85
% change from baseline (adjusted mean)	-3.1	-3.4	-3.0	-3.5	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI) ^c	0.0 (-0.9, 0.8)	0.1 (-0.8, 0.9)	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI) ^c	-2.4 (-3.3, -1.5) ^d	-2.7 (-3.6, -1.8) ^d	--	--	--

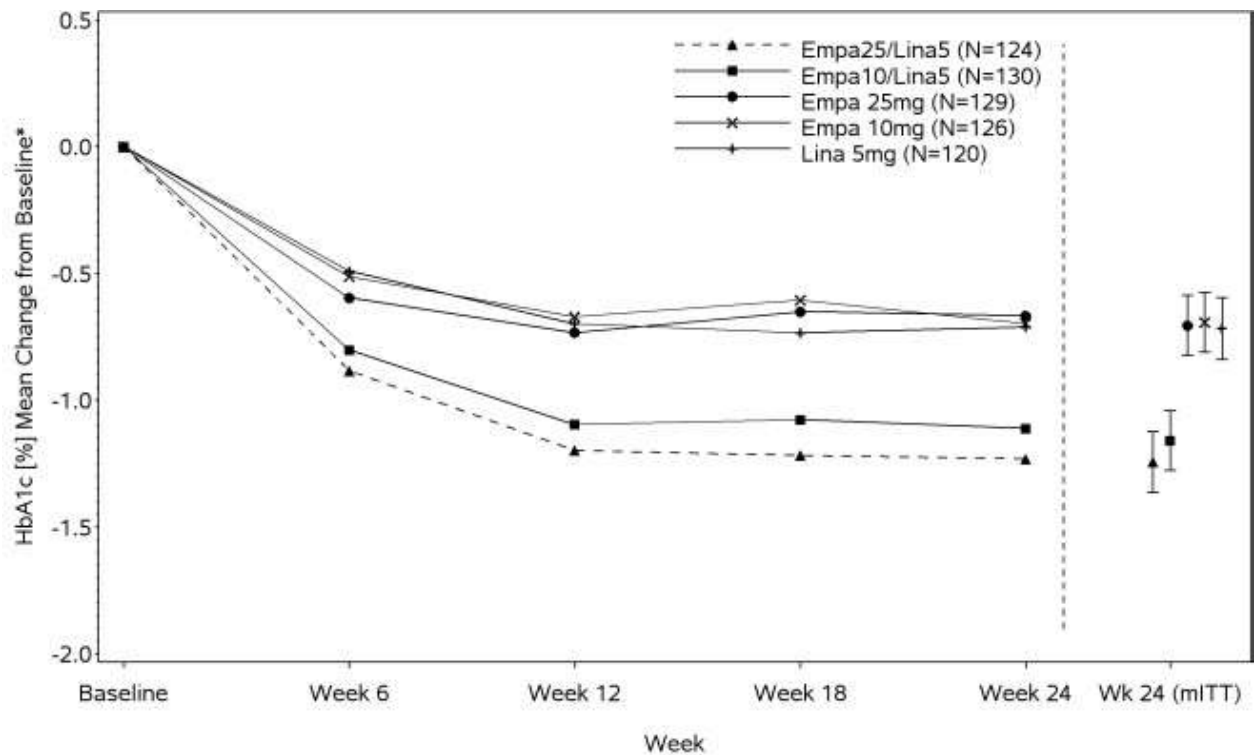
^aFull analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.

^bPatients with HbA1c above 7% at baseline: Empagliflozin and linagliptine tablets 25 mg/5 mg, n=123; Empagliflozin and linagliptine tablets 10 mg/5 mg, n=128; empagliflozin 25 mg, n=132; empagliflozin 10 mg, n=125; linagliptin 5 mg, n=119. Non-completers were considered failures (NCF).

^cFull analysis population using last observation carried forward. ANCOVA model included treatment, renal function, region, baseline weight, and baseline HbA1c.

^dp<0.001 for FPG; p<0.0001 for HbA1c and body weight .

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

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

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

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

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo

= 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators, respectively and the mean eGFR was 74 mL/min/1.73 m². At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), sulfonylurea (43%) and dipeptidyl peptidase-4 inhibitor (11%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

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

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

Table 5 Treatment Effect for the Primary Composite Endpoint and its Components^a

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

^aTreated set (patients who had received at least one dose of study drug)

^bp-value for superiority (2-sided) 0.04

^cTotal number of events

Figure 4 Estimated Cumulative Incidence of First MACE

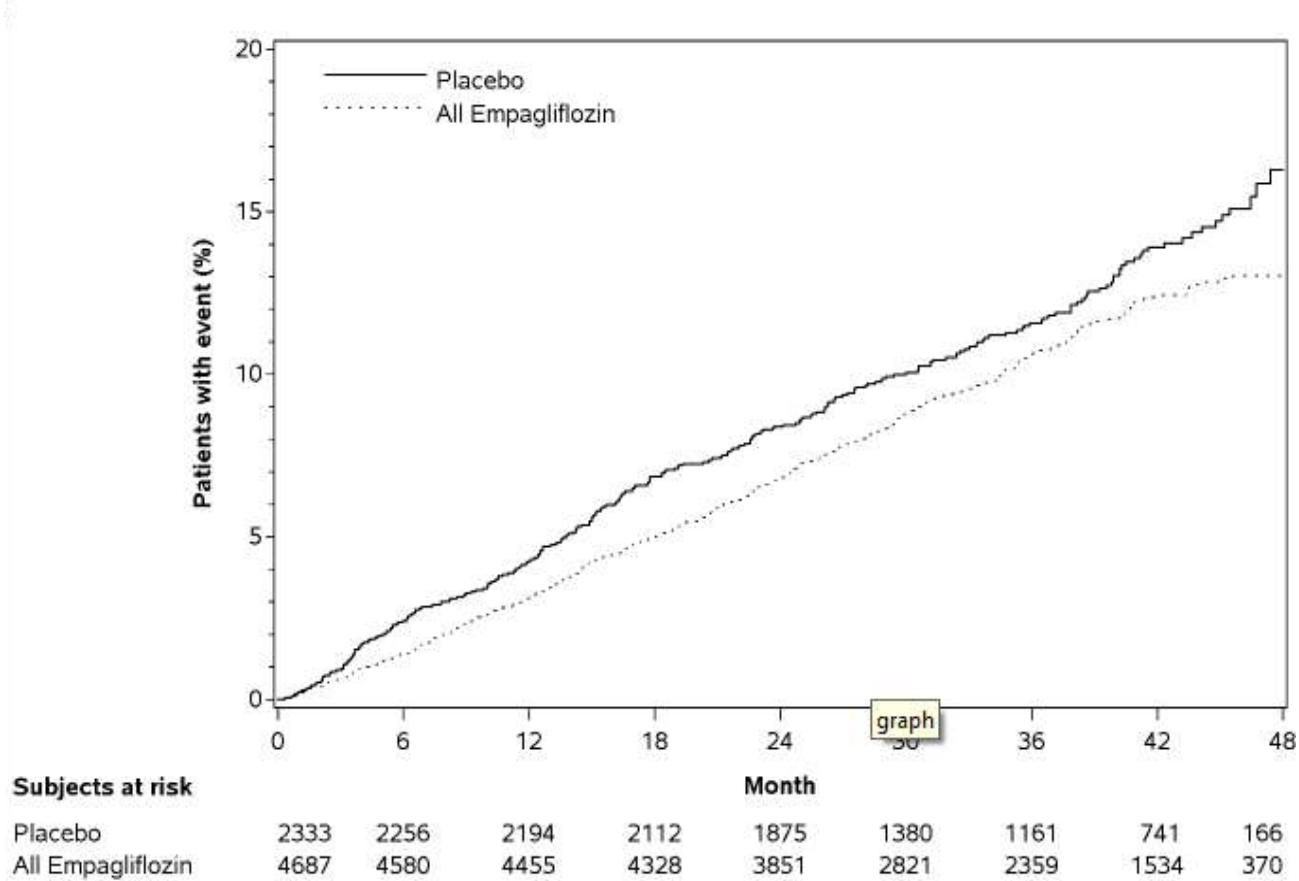
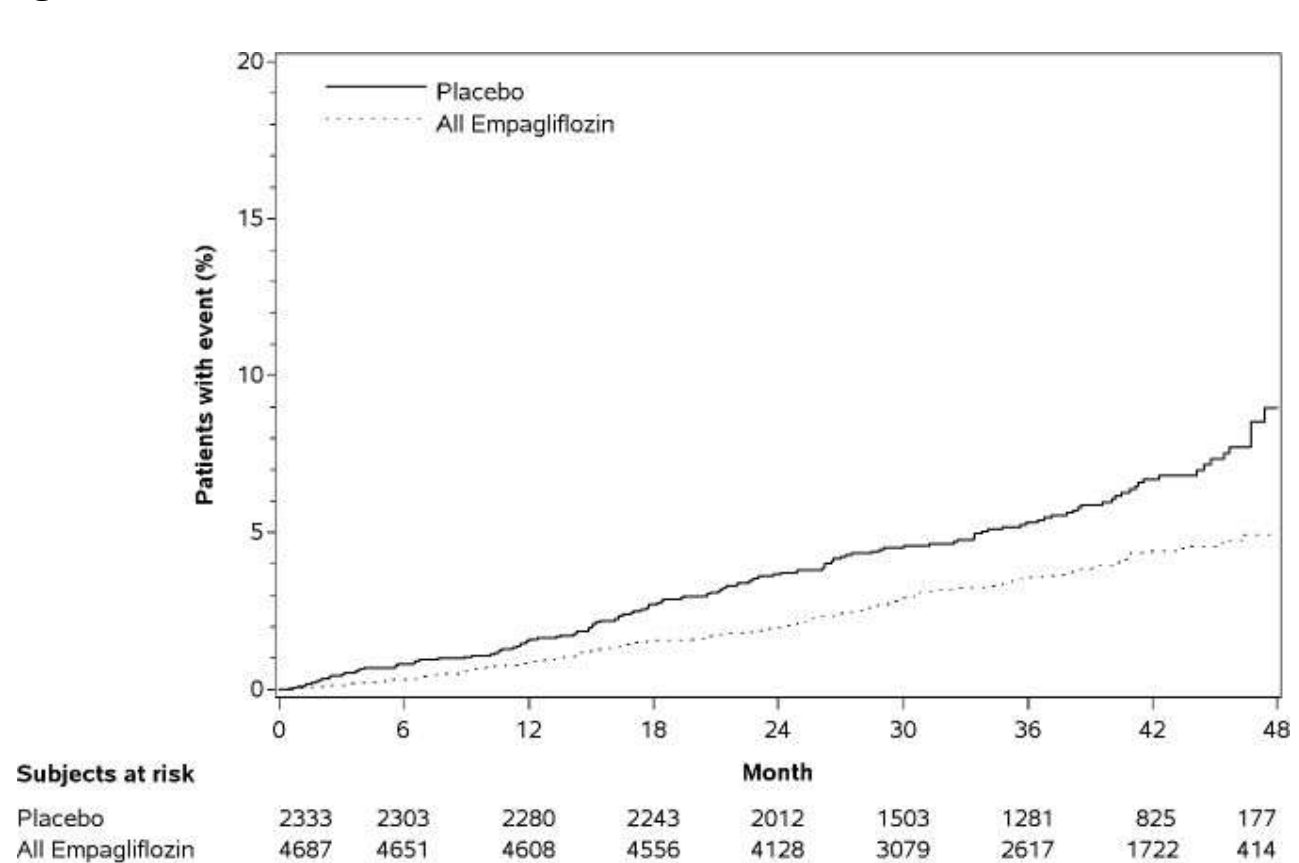


Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups.

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

Linagliptin Cardiovascular Safety Trials

CARMELINA

The cardiovascular risk of linagliptin was evaluated in CARMELINA, a multinational, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3494) to placebo (N=3485) in adult patients with type 2 diabetes mellitus and a history of established macrovascular and/or renal disease. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and placebo when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 2.2 years and vital status was obtained for 99.7% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes, with HbA1c of 6.5% to 10%, and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function by eGFR and Urinary Albumin Creatinine Ratio (UACR) criteria (42% of enrolled population), or both (18% of enrolled population).

At baseline the mean age was 66 years and the population was 63% male, 80% Caucasian, 9% Asian, and 6% Black. Mean HbA1c was 8.0% and mean duration of type 2 diabetes mellitus was 15 years. The trial population included 17% patients ≥ 75 years of age and 62% patients with renal impairment defined as eGFR < 60 mL/min/1.73 m². The mean eGFR was 55 mL/min/1.73 m² and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m²), 47% of patients had moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²) and 15% of patients had severe renal impairment (eGFR < 30 mL/min/1.73 m²). Patients were taking at least one antidiabetic drug (97%), and the most common were insulin and analogues (57%), metformin (54%) and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% on statin, and aspirin (62%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 434

patients on linagliptin and 420 patients on placebo experienced MACE. The incidence rate of MACE in both treatment arms: 56.3 MACE per 1000 patient-years on placebo vs. 57.7 MACE per 1000 patient-years on linagliptin. The estimated hazard ratio for MACE associated with linagliptin relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3.

CAROLINA

The cardiovascular risk of linagliptin was evaluated in CAROLINA, a multi-center, multinational, randomized, double-blind parallel group trial comparing linagliptin (N=3023) to glimepiride (N=3010) in adult patients with type 2 diabetes mellitus and a history of established cardiovascular disease and/or multiple cardiovascular risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and glimepiride when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes with insufficient glycemic control (defined as HbA1c of 6.5% to 8.5% or 6.5% to 7.5% depending on treatment-naïve, on monotherapy or on combination therapy), and were defined to be at high cardiovascular risk with previous vascular disease, evidence of vascular related end-organ damage, age ≥ 70 years, and/or two cardiovascular risk factors (duration of diabetes >10 years, systolic blood pressure >140 mmHg, current smoker, LDL cholesterol ≥ 135 mg/dL).

At baseline the mean age was 64 years and the population was 60% male, 73% Caucasian, 18% Asian, and 5% Black. The mean HbA1c was 7.15% and mean duration of type 2 diabetes was 7.6 years. The trial population included 34% patients ≥ 70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m². The mean eGFR was 77 mL/min/1.73 m². Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial

infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 356 patients on linagliptin and 362 patients on glimepiride experienced MACE. The incidence rate of MACE in both treatment arms: 20.7 MACE per 1000 patient-years on linagliptin vs. 21.2 MACE per 1000 patient-years on glimepiride. The estimated hazard ratio for MACE associated with linagliptin relative to glimepiride was 0.98 with a 95% confidence interval of (0.84, 1.14). The upper bound of this confidence interval, 1.14, excluded the risk margin of 1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose USP/NF
Lactose Monohydrate USP/NF
Croscarmellose Sodium, USP/NF
Ferric Oxide Yellow USP/NF
Hydroxypropyl Cellulose, USP/NF
Purified Water IHS/USP/Ph.Eur
Purified Water IHS/USP/Ph.Eur@ (If required)
Colloidal Silicon Dioxide USP/NF
Magnesium Stearate, USP/NF
Linagliptin, IH
Mannitol, USP
Corn Starch, USP-NF
Croscarmellose sodium, USP/NF
Copovidone, USP/NF
Magnesium Stearate, USP/NF

6.2 Shelf life

2 years.

6.3 Special precautions for storage

Store below 30°C.

6.4 Nature and contents of container

30's Count HDPE Container

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Supplier	Manufacturer
-----------------	---------------------

Hetero Labs Limited 7-2-A2, Hetero Corporate Industrial Estates Sanath Nagar, Hyderabad-500 018 Telangana, India Tel. No.: +91 40 23704923/ 24/25 Fax:+91 40 23704035, 23813359 Email: contact@heterodrugs.com	Annora Pharma Private Limited Sy.No.261, Annaram (V), Gummadidala (M), Sangareddy (D), Telangana State, India.
--	--

8. MARKETING AUTHORISATION NUMBER

H2026/CTD12833/27613

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2026 May 12

10. DATE OF REVISION OF THE TEXT

2026 May 12