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

XILINGIO®

FDC of Empagliflozin and Linagliptin Film-coated Tablets

10 mg/5 mg, 25 mg/5 mg

1.   INDICATIONS AND USAGE

XILINGIO® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use
XILINGIO® is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.2)]*.

XILINGIO® 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 XILINGIO® *[see Warnings and Precautions (5.1)]*.

XILINGIO® 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 m^2. XILINGIO® is likely to be ineffective in this setting based upon its mechanism of action.

2.   DOSAGE AND ADMINISTRATION

2.1   Prior to Initiation of XILINGIO®
* Assess renal function before initiating XILINGIO® and as clinically indicated *[see Warnings and Precautions (5.3)]*.
* In patients with volume depletion, correct this condition before initiating XILINGIO® *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)]*.

2.2   Recommended Dosage

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

2.3   Dosage Recommendations in Patients with Renal Impairment

XILINGIO® is not recommended for use in patients with an eGFR less than 30 mL/min/1.73 m^2 and contraindicated in patients on dialysis *[see Indications and Usage (1), Contraindications (4), Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3.   DOSAGE FORMS AND STRENGTHS

XILINGIO® tablets are a combination of empagliflozin and linagliptin available as:

- 10 mg empagliflozin/5 mg linagliptin are pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5".

- 25 mg empagliflozin/5 mg linagliptin are pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

4.   CONTRAINDICATIONS

- Patients on dialysis *[see Use in Specific Populations (8.6)]*.
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in XILINGIO®, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (5.8) and Adverse Reactions (6)]*.

5.   WARNINGS AND PRECAUTIONS

5.1   Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial *[see Clinical Studies (14)]*, 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 XILINGIO® 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 XILINGIO®.

5.2   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. XILINGIO® is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with XILINGIO® 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 XILINGIO® may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, XILINGIO® 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 XILINGIO®, 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 XILINGIO® for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing XILINGIO® 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 XILINGIO®.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue XILINGIO® and seek medical attention immediately if signs and symptoms occur.

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

5.4 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with XILINGIO®.

5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in

patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with XILINGIO® 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 XILINGIO®, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.7   Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections *[see Adverse Reactions (6.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

5.8   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 XILINGIO®.

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

If a hypersensitivity reaction occurs, discontinue XILINGIO®, treat promptly per standard of care, and monitor until signs and symptoms resolve. XILINGIO® is contraindicated in patients with hypersensitivity to linagliptin, empagliflozin, or any of the excipients in XILINGIO® *[see Contraindications (4)]*.

5.9   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.

5.10   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 *[see Clinical Studies (14)]*, 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 XILINGIO®. If bullous pemphigoid is suspected, XILINGIO® should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.11 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 XILINGIO® 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 XILINGIO®.

6.   ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:
- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[see Warnings and Precautions (5.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.9)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.10)]*
- Heart Failure *[see Warnings and Precautions (5.11)]*

6.1 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 and Linagliptin
The safety of concomitantly administered empagliflozin (daily dose 10 mg or 25 mg) and linagliptin (daily dose 5 mg) has been evaluated in a total of 1363 patients with type 2 diabetes treated for up to 52 weeks in active-controlled clinical trials. The most common adverse reactions with concomitant administration of empagliflozin and linagliptin based on a pooled analyses of these studies are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin and Linagliptin

Adverse Reactions	XILINGIO® (%) 10 mg/5 mg n=272	XILINGIO® (%) 25 mg/5 mg n=273
Urinary tract infection[a]	12.5	11.4
Nasopharyngitis	5.9	6.6
Upper respiratory tract infection	7.0	7.0

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Empagliflozin
Adverse reactions that occurred in ≥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 XILINGIO® plus metformin.

Linagliptin
Adverse reactions reported in ≥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 studies 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.

Hypoglycemia
Table 2 summarizes the reports of hypoglycemia with empagliflozin and linagliptin over a treatment period of 52 weeks.

Table 2 Incidence of Overall[a] and Severe[b] Hypoglycemic Adverse Reactions

Add-on to Metformin (52 weeks)	XILINGIO® (%) 10 mg/5 mg (n=136)	XILINGIO® (%) 25 mg/5 mg (n=137)
Overall	2.2	3.6
Severe	0	0

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL or requiring assistance
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

Laboratory Tests
Empagliflozin and Linagliptin
Changes in laboratory findings in patients treated with the combination of empagliflozin and linagliptin included increases in cholesterol and hematocrit compared to baseline.

Empagliflozin
Increases in Serum Creatinine and Decreases in eGFR: Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

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

6.2   Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of linagliptin and empagliflozin. 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 *[see Indications and Usage (1)]*, constipation, 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)

7.   DRUG INTERACTIONS

Table 3   Clinically Relevant Interactions with XILINGIO®

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating XILINGIO®, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating XILINGIO®. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	Empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial.
Intervention	Coadministration of XILINGIO® 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.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.
Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	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.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

8.   USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on animal data showing adverse renal effects, from empagliflozin, XILINGIO® is not recommended during the second and third trimesters of pregnancy.

The limited available data with XILINGIO®, 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 *(see Clinical Considerations).*

In animal studies, empagliflozin, a component of XILINGIO®, 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 *(see Data).*

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 XILINGIO®.

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.

8.2   Lactation

Risk Summary
There is no information regarding the presence of XILINGIO®, 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 *(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 XILINGIO® 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.

8.4   Pediatric Use

Safety and effectiveness of XILINGIO® have not been established in pediatric patients.

8.5   Geriatric Use

XILINGIO®
Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older *[see Warnings and Precautions (5.3)]*.

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.

8.6   Renal Impairment

Empagliflozin
The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.3)]*, 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 end stage renal disease (ESRD) on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. Empagliflozin is contraindicated in patients on dialysis *[see Indications and Usage (1) and Contraindications (4)]*.

8.7   Hepatic Impairment

XILINGIO® may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10.   OVERDOSAGE

In the event of an overdose with XILINGIO®, 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.

11.   DESCRIPTION

XILINGIO® tablets for oral use contains: 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-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:
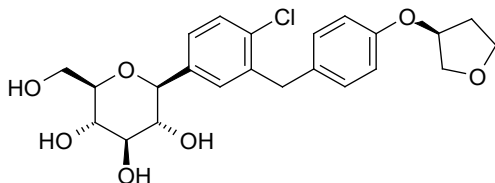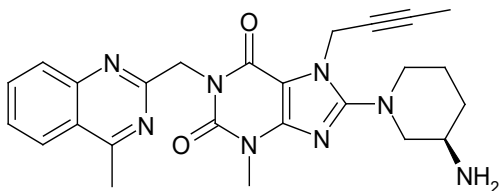

Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

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)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

The molecular formula is $C_{25}H_{28}N_8O_2$ 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.

XILINGIO®
XILINGIO® tablets are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin. The inactive ingredients of XILINGIO® 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).

12.   CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XILINGIO®
XILINGIO® contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Empagliflozin
Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Linagliptin
Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic 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.

12.2 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.

12.3 Pharmacokinetics

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

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
XILINGIO®: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of XILINGIO® in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patientswith kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and kidney failure/ESRD compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

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 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$_{\tau,ss}$ 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 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

XILINGIO®: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of XILINGIO® 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 *[see Use in Specific Populations (8.5)]*.

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 *[see Use in Specific Populations (8.5)]*.

Drug Interactions

Pharmacokinetic drug interaction studies with XILINGIO® have not been performed; however, such studies have been conducted with the individual components of XILINGIO® (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'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9 and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit

any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, 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 C_{max} Ratios [reference lines indicate 100% (80% - 125%)]**
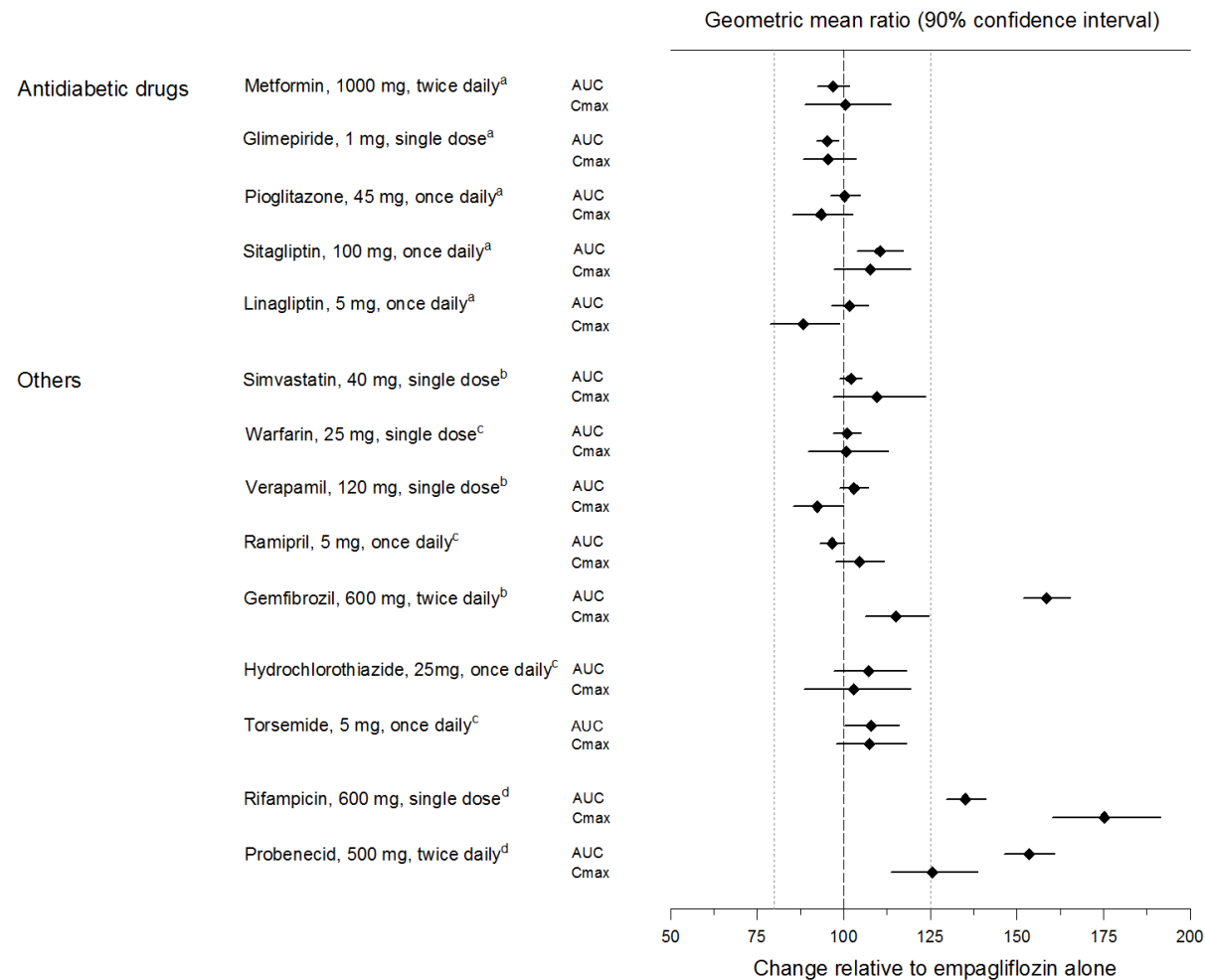
[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

17

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2   **Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]**
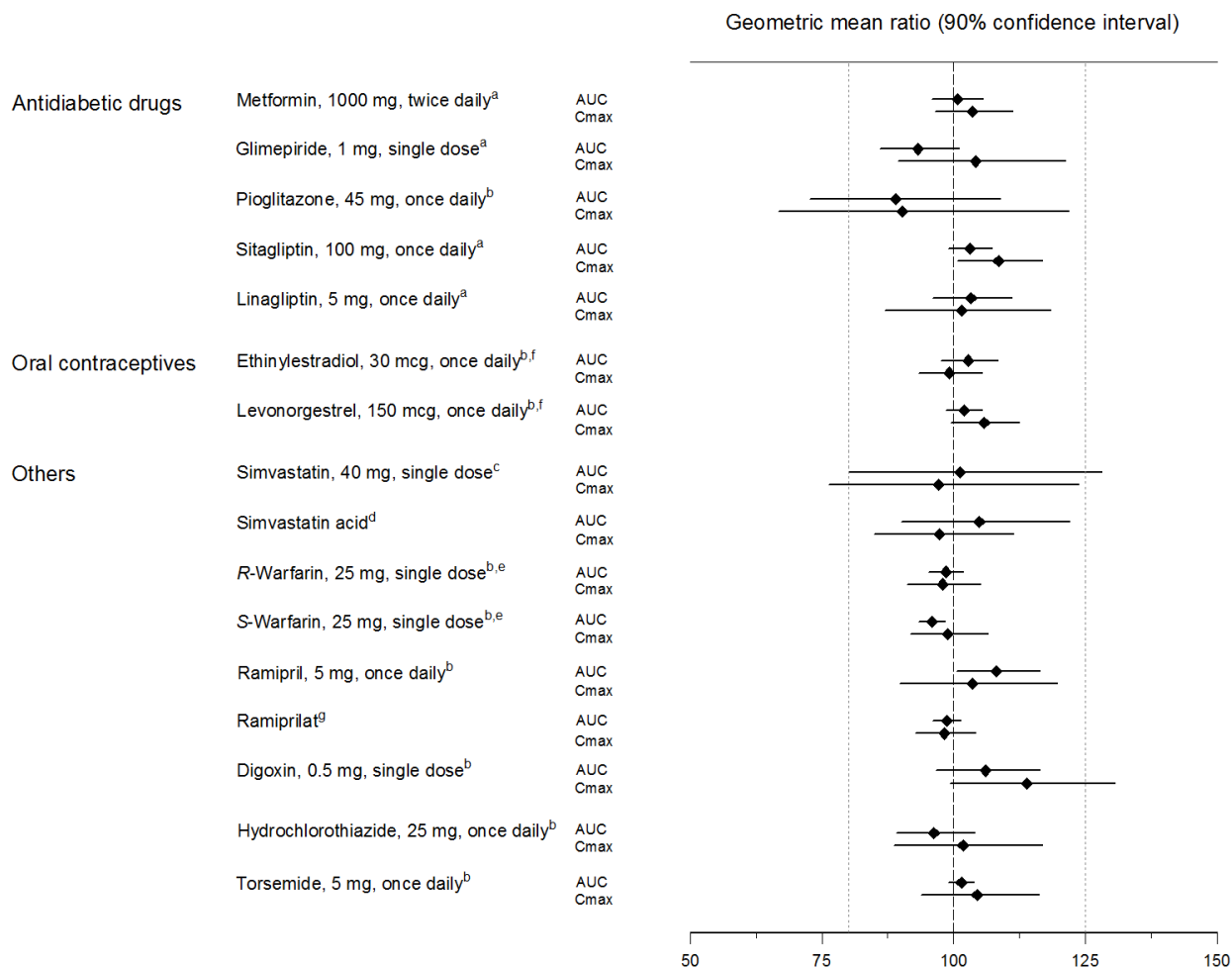
[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

Linagliptin
<u>*In vitro* Assessment of Drug Interactions</u>
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.

<u>*In vivo* Assessment of Drug Interactions</u>
Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations *[see Drug Interactions (7)]. In vivo* studies indicated evidence of a low propensity for

18

causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 4   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

[a]Multiple dose (steady-state) unless otherwise noted
[b]For information regarding clinical recommendations *[see Drug Interactions (7)]*.
[c]Single dose
[d]AUC = 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 5   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 metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 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

[a]Multiple dose (steady-state) unless otherwise noted
[b]Single dose
[c]AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
[d]AUC=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

13.   NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

XILINGIO®

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

14. CLINICAL STUDIES

XILINGIO® 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 (see Table 6, Figure 3). Treatment with XILINGIO® 25 mg/5 mg or XILINGIO® 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 6   Glycemic Parameters at 24 Weeks in a Study Comparing XILINGIO® to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

|	XILINGIO® 10 mg/5 mg	XILINGIO® 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]	--	--	--

Figure 3   Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)
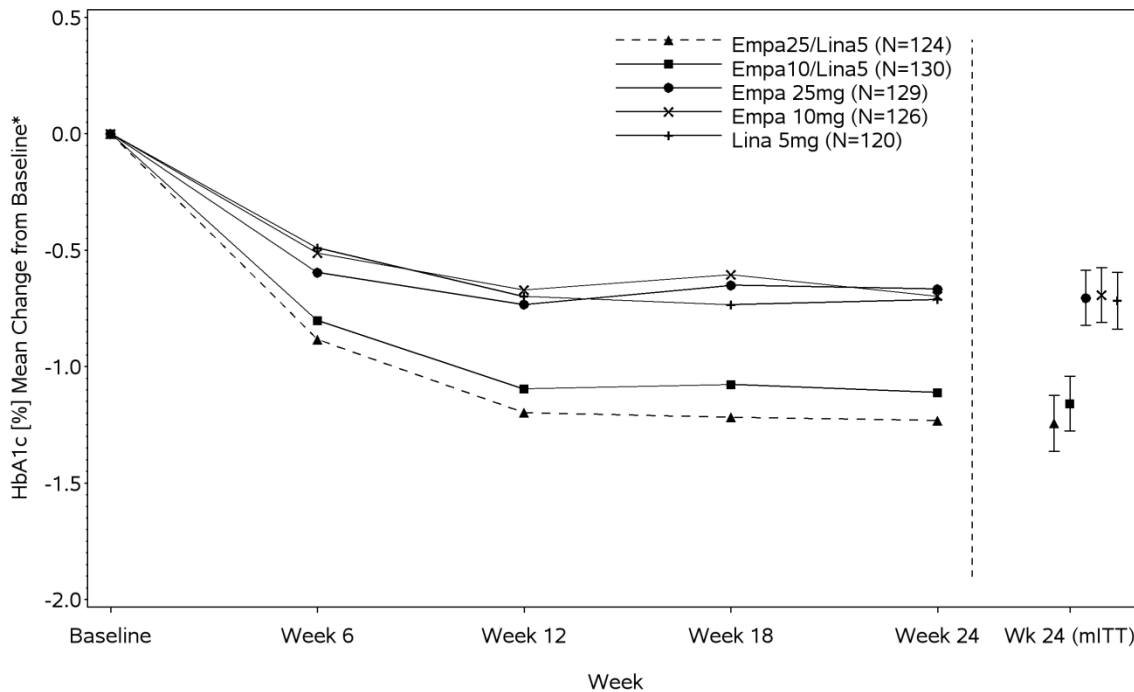
*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

Cardiovascular safety

In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) by 14% when added to standard of care in adults with T2DM and established CV disease. This result was driven by a 38% reduction in CV death, with no significant difference in the risk of non-fatal myocardial infarction or non-fatal stroke.

In the CARMELINA study, linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [Hazard Ratio (HR)=1.02; (95% CI 0.89, 1.17); p=0.0002 for non-inferiority], or the risk of combined endpoint of renal death, ESRD, 40% or more sustained decrease in eGFR [HR=1.04; (95% CI 0.89, 1.22)], when added to standard of care in adult patients with T2DM with increased CV risk evidenced by a history of established macrovascular or renal disease. In addition, linagliptin did not increase the risk of hospitalization for heart failure [HR=0.90; (95% CI 0.74, 1.08)]. No increased risk of CV death or all-cause mortality was observed. Safety data from this study was in line with previous known safety profile of linagliptin.

In the CAROLINA study, linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [Hazard Ratio (HR)=0.98; (95% CI 0.84, 1.14); p<0.0001 for

non-inferiority], when added to standard of care in adult patients with T2DM with increased CV risk compared to glimepiride. For the entire treatment period the rate of patients with moderate or severe hypoglycaemia was 6.5% on linagliptin versus 30.9% on glimepiride, severe hypoglycaemia (requiring assistance) occurred in 0.3% of patients on linagliptin versus 2.2% on glimepiride.

There have been no clinical studies establishing conclusive evidence of XILINGIO®'s effect on cardiovascular morbidity and mortality.

16.   HOW SUPPLIED/STORAGE AND HANDLING

This product is supplied as follows:
Pack of 90 (9X10) Film Coated tablets.
Each blister contains 10 tablets.

Storage:
Store in a safe place out of the reach of children.
Do not store above 30ºC.

Shelf Life:
36 Months

17.   PATIENT COUNSELING INFORMATION

Pancreatitis
Inform patients that acute pancreatitis has been reported during use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue XILINGIO® promptly and contact their healthcare provider if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Ketoacidosis
Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue XILINGIO® and seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

Volume Depletion
Inform patients that symptomatic hypotension may occur with XILINGIO® and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.3)]*. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Serious Urinary Tract Infections
Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the incidence of hypoglycemia is increased when XILINGIO® is used in combination with an insulin secretagogue (e.g.,sulfonylurea) or insulin, and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.5)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin, a component of XILINGIO®. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)
Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions
Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin or empagliflozin, components of XILINGIO®. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking XILINGIO® and seek medical advice promptly *[see Warnings and Precautions (5.8)]*.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.9)]*.

Bullous Pemphigoid
Inform patients that bullous pemphigoid has been reported during use of linagliptin. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.10)]*.

Heart Failure
Inform patients of the signs and symptoms of heart failure. Before initiating XILINGIO®, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.11)]*.

Laboratory Tests
Inform patients that elevated glucose in urinalysis is expected when taking XILINGIO®.

Pregnancy

Advise pregnant patients, and patients of reproductive potential of the potential risk to a fetus with treatment with XILINGIO® *[see Use in Specific Populations (8.1)]*. Instruct patients to report pregnancies to their healthcare provider as soon as possible.

Lactation
Advise patients that breastfeeding is not recommended during treatment with XILINGIO® *[see Use in Specific Populations (8.2)]*.

Missed Dose
Instruct patients to take XILINGIO® only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Manufacturer:

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173, 55216 Ingelheim am Rhein,
Germany

 OR

Rottendorf Pharma GmbH,
Ostenfelder Str. 51-61, 59320
Ennigerloh, Germany

Imported in India by:

Boehringer Ingelheim India Private Limited
Building no. D-5, Gala No. 1 to 5, Shree Arihant Compound,
Ground floor, Reti Bunder Road, Kalher,
Bhiwandi, Thane,
Maharashtra (India) – 421302

Marketed in India by:

TORRENT PHARMACEUTICALS LIMITED,
Indrad-382 721, Dist. Mehsana, INDIA

Marketing Authorization Number: IMP-236/2017

Date of First Authorisation: 16-Oct-2017

Source: US pack insert dated Mar 2022 (20210803)

India pack insert version: 31-May-2023