HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GLYXAMBI safely and effectively. See full prescribing information for GLYXAMBI.

GLYXAMBI® (empagliflozin and linagliptin) tablets, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Warnings and Precautions	
Pancreatitis (5.1)	7/2019
Ketoacidosis (5.4)	1/2020
Bullous Pemphigoid (5.13)	7/2019
Macrovascular Outcomes – Removed	7/2019

----------INDICATIONS AND USAGE----------

GLYXAMBI is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, 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. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established (1)

Limitations of Use
- Not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1)
- Has not been studied in patients with a history of pancreatitis (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of GLYXAMBI is 10 mg empagliflozin/5 mg linagliptin once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily (2.1)
- Assess renal function before initiating GLYXAMBI. Do not initiate GLYXAMBI if eGFR is below 45 mL/min/1.73 m^2 (2.2)
- Discontinue GLYXAMBI if eGFR falls persistently below 45 mL/min/1.73 m^2 (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets:
10 mg empagliflozin/5 mg linagliptin
25 mg empagliflozin/5 mg linagliptin (3)

----------CONTRAINDICATIONS----------

- Severe renal impairment, end-stage renal disease, or dialysis (4)
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)

----------WARNINGS AND PRECAUTIONS----------

- *Pancreatitis:* There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI. (5.1)
- *Heart Failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of GLYXAMBI in patients who have known risk factors for heart failure. Monitor for signs and symptoms. (5.2)
- *Hypotension:* Before initiating GLYXAMBI assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue GLYXAMBI, evaluate and treat promptly. Before initiating GLYXAMBI, consider risk factors for ketoacidosis. Patients on GLYXAMBI may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.4)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.5)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.6)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating GLYXAMBI. (5.7)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.8)
- *Genital Mycotic Infections:* Monitor and treat as appropriate (5.9)
- *Hypersensitivity Reactions:* Discontinue GLYXAMBI, treat promptly, and monitor until signs and symptoms resolve. (5.10)
- *Increased LDL-C:* Monitor and treat as appropriate (5.11)
- *Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.12)
- *Bullous Pemphigoid:* There have been reports of bullous pemphigoid requiring hospitalization. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue GLYXAMBI. (5.13)

----------ADVERSE REACTIONS----------

- The most common adverse reactions associated with GLYXAMBI (a 5% or greater incidence) were urinary tract infections, nasopharyngitis, and upper respiratory tract infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- *Lactation:* GLYXAMBI is not recommended when breastfeeding (8.2)
- *Pediatric Patients*: Safety and effectiveness of GLYXAMBI in pediatric patients have not been established (8.4)
- *Geriatric Patients:* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.3, 5.5, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLYXAMBI 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 *[see Clinical Studies (14.2)]*. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use

GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis *[see Warnings and Precautions (5.4)]*.

GLYXAMBI 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 GLYXAMBI *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of GLYXAMBI is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. In patients tolerating GLYXAMBI, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.

In patients with volume depletion, correcting this condition prior to initiation of GLYXAMBI is recommended *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5) and Patient Counseling Information (17)]*.

No studies have been performed specifically examining the safety and efficacy of GLYXAMBI in patients previously treated with other oral antihyperglycemic agents and switched to GLYXAMBI. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of GLYXAMBI and periodically thereafter.

GLYXAMBI should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

GLYXAMBI should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.3, 5.5) and Use in Specific Populations (8.6)]*.

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3 DOSAGE FORMS AND STRENGTHS

GLYXAMBI is a combination of empagliflozin and linagliptin. GLYXAMBI is available in the following dosage forms and strengths:

- 10 mg empagliflozin/5 mg linagliptin tablets 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 tablets 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

GLYXAMBI is contraindicated in patients with:

- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity *[see Warnings and Precautions (5.10) 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 (14.3)]*, 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 GLYXAMBI 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 GLYXAMBI.

5.2 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 GLYXAMBI 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 GLYXAMBI.

5.3 Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating GLYXAMBI, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension

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after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

5.4 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in 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. GLYXAMBI is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

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

Consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI 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 GLYXAMBI.

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

5.5 Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction *[see Warnings and Precautions (5.3)]* and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating GLYXAMBI, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing GLYXAMBI in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat

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exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue GLYXAMBI promptly and institute treatment.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating GLYXAMBI *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of GLYXAMBI and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of GLYXAMBI is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4) and Use in Specific Populations (8.6)]*.

5.6 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)]*.

5.7 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 GLYXAMBI.

5.8 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 GLYXAMBI 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 GLYXAMBI, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.9 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.

5.10 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of GLYXAMBI). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred 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 GLYXAMBI.

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

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

5.11 Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.12 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.

5.13 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 (14.3)]*, 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 GLYXAMBI. If bullous pemphigoid is suspected, GLYXAMBI should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

6 ADVERSE REACTIONS

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

- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Heart Failure *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Ketoacidosis *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (5.5)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.6)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.7)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.8)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.9)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.10)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.11)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.12)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

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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

	GLYXAMBI 10 mg/5 mg n=272	**GLYXAMBI 25 mg/5 mg n=273**
	n (%)	**n (%)**
Urinary tract infection[a]	34 (12.5)	31 (11.4)
Nasopharyngitis	16 (5.9)	18 (6.6)
Upper respiratory tract infection	19 (7.0)	19 (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.

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.

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

Add-on to Metformin (52 weeks)	**GLYXAMBI 10 mg/5 mg (n=136)**	**GLYXAMBI 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

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 *[see Warnings and Precautions (5.11)]*. 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.

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.

- Acute Pancreatitis, including Fatal Pancreatitis *[see Indications and Usage (1)]*
- Ketoacidosis
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Hypersensitivity Reactions including Anaphylaxis, Angioedema, and Exfoliative Skin Conditions
- Severe and Disabling Arthralgia
- Bullous Pemphigoid
- Skin Reactions (e.g., rash, urticaria)

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- Mouth Ulceration, Stomatitis
- Rhabdomyolysis

7 DRUG INTERACTIONS

7.1 Drug Interactions with Empagliflozin

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions (5.3)]*.

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

7.2 Drug Interactions with Linagliptin

Inducers of P-glycoprotein or CYP3A4 Enzymes

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. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

7.3 Insulin or Insulin Secretagogues

Coadministration of GLYXAMBI 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 *[see Warnings and Precautions (5.7)]*.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The limited available data with GLYXAMBI, 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, adverse renal changes were observed in rats when empagliflozin was 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 during the period of organogenesis at exposures approximately 253 and 353 times the clinical exposure *(see Data).*

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% 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 2-4% and 15-20%, 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 post-natal development study was not conducted with the combined components of GLYXAMBI.

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

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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 GLYXAMBI, 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 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 -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 GLYXAMBI in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

GLYXAMBI

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

Empagliflozin

No empagliflozin dosage change is recommended based on age *[see Dosage and Administration (2)]*. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and

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older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Linagliptin
There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
Empagliflozin
The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.3, 5.5)]*.

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.5)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

8.7 Hepatic Impairment
GLYXAMBI may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

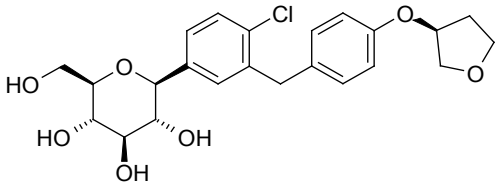
10 OVERDOSAGE
In the event of an overdose with GLYXAMBI, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

11 DESCRIPTION
GLYXAMBI tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and linagliptin.

Empagliflozin
Empagliflozin is an orally-active inhibitor of the sodium-glucose co-transporter (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:



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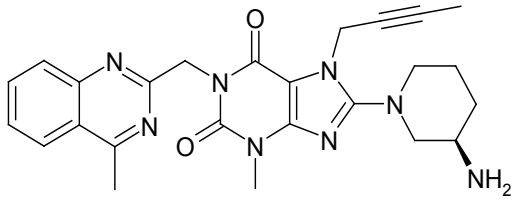
Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Linagliptin
Linagliptin is an orally-active 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.

GLYXAMBI
GLYXAMBI tablets for oral administration are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin. The inactive ingredients of GLYXAMBI 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

GLYXAMBI
GLYXAMBI combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: 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

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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

GLYXAMBI

The results of the bioequivalence study in healthy subjects demonstrated that GLYXAMBI (25 mg empagliflozin/5 mg linagliptin) combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and linagliptin as individual 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,

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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.

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.

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. 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

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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. Renal clearance at steady state was approximately 70 mL/min.

Specific Populations
Renal Impairment
GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in renally impaired patients have not been performed *[see Dosage and Administration (2.2)]*.

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 subjects with kidney failure/end stage renal disease (ESRD) patients, 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 subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects 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
GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in hepatically impaired patients have not been performed.

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Empagliflozin: In subjects 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)]*.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or linagliptin after administration of GLYXAMBI in pediatric patients have not been performed.

Drug Interactions

Pharmacokinetic drug interaction studies with GLYXAMBI have not been performed; however, such studies have been conducted with the individual components of GLYXAMBI (empagliflozin and linagliptin).

Empagliflozin

In vitro Assessment of Drug Interactions

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. 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

No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. 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

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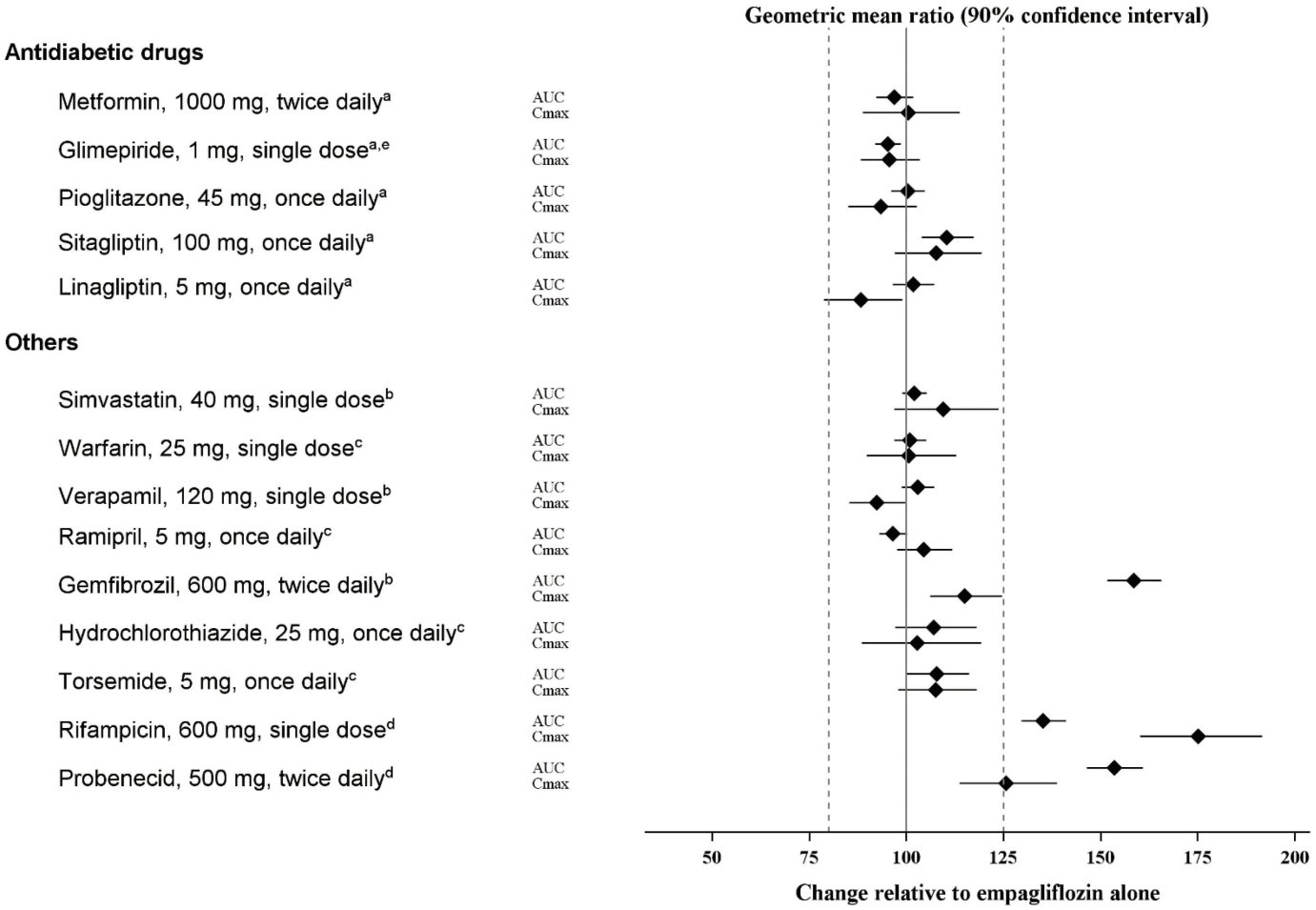
hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration 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
[e]Coadministration of empagliflozin 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 *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.

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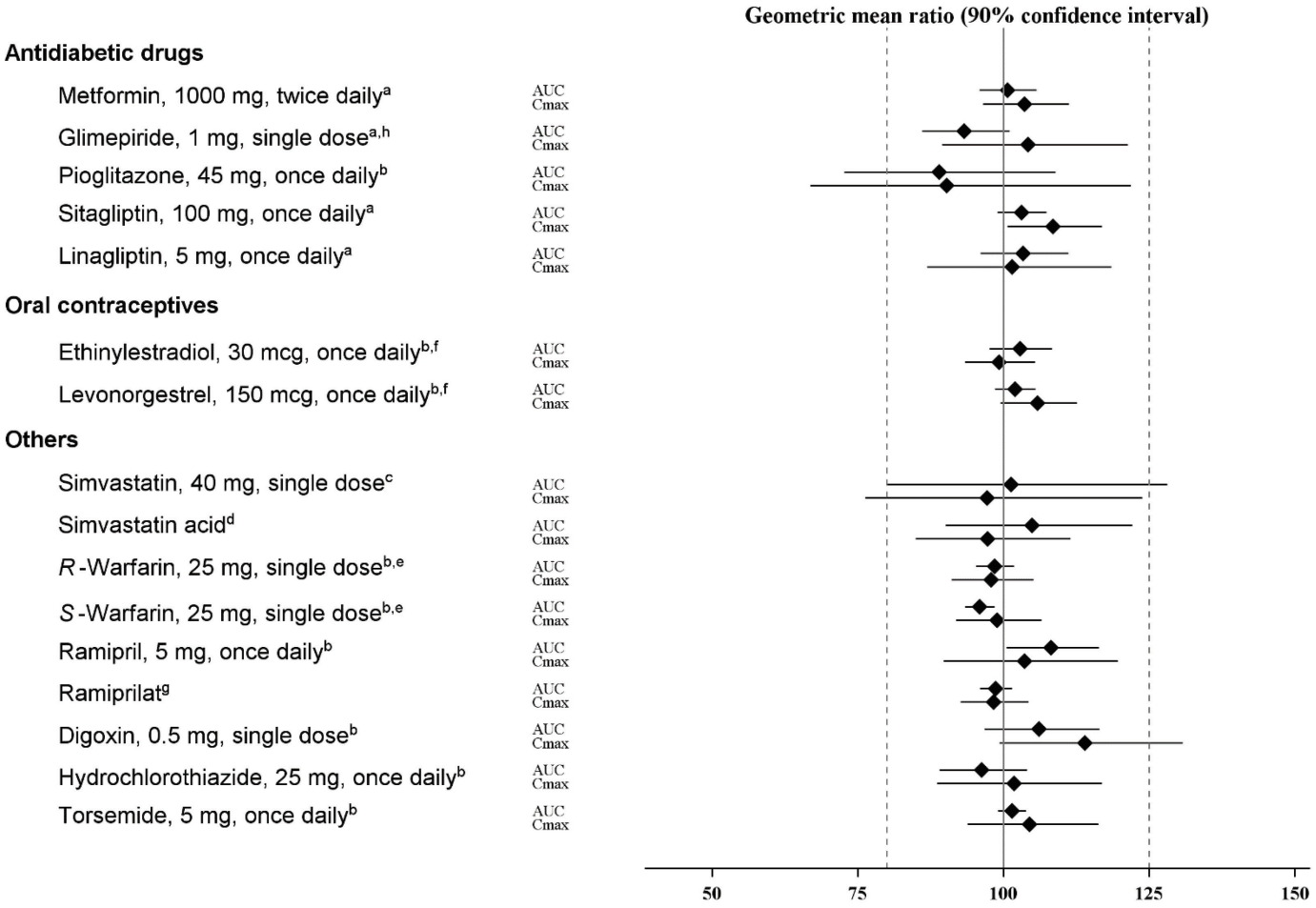
Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

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
[h]Coadministration of empagliflozin 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 *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.

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. For patients requiring use of such drugs, an alternative to linagliptin is

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strongly recommended. *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). No dose adjustment of linagliptin is recommended based on results of the described pharmacokinetic studies.

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

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

[a]Multiple dose (steady state) unless otherwise noted
[b]Coadministration of linagliptin 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 *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.
[c]For information regarding clinical recommendations *[see Drug Interactions (7.2)]*.
[d]Single dose
[e]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 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug[a]	Dosing of Linagliptin[a]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC[d]	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide[b]	1.75 mg[c]	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[c]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93[e] 1.03[e]	1.00 1.01 1.04[e] 1.15[e]
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]Coadministration of linagliptin 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 *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.
[c]Single dose
[d]AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
[e]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

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GLYXAMBI

No animal studies have been conducted with the combination of empagliflozin and linagliptin to evaluate carcinogenesis, mutagenesis, or impairment of fertility. 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).

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14 CLINICAL STUDIES

14.1 GLYXAMBI 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 5, Figure 3). Treatment with GLYXAMBI 25 mg/5 mg or GLYXAMBI 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.

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Table 5 Glycemic Parameters at 24 Weeks in a Study Comparing GLYXAMBI to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	GLYXAMBI 10 mg/5 mg	GLYXAMBI 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]	--	--	--

[a]Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.
[b]Patients with HbA1c above 7% at baseline: GLYXAMBI 25 mg/5 mg, n=123; GLYXAMBI 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).
[c]Full analysis population using last observation carried forward. ANCOVA model included treatment, renal function, region, baseline weight, and baseline HbA1c.
[d]$p<0.001$ for FPG; $p<0.0001$ for HbA1c and body weight

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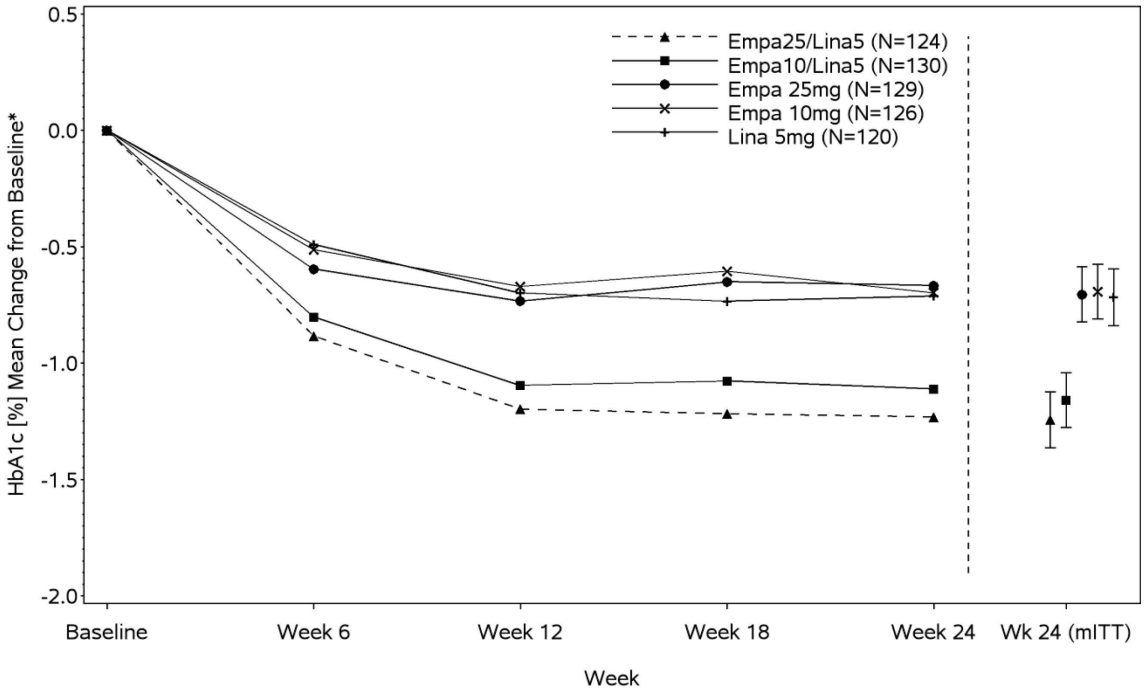
Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)



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

14.2 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. However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has not been established. 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, multi-national, 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 m^2. 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%).

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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 nonfatal myocardial infarction (MI) or a nonfatal 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 non-inferiority 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 (see Table 6 and Figure 4 and 5). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 6 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)

[a]Treated set (patients who had received at least one dose of study drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

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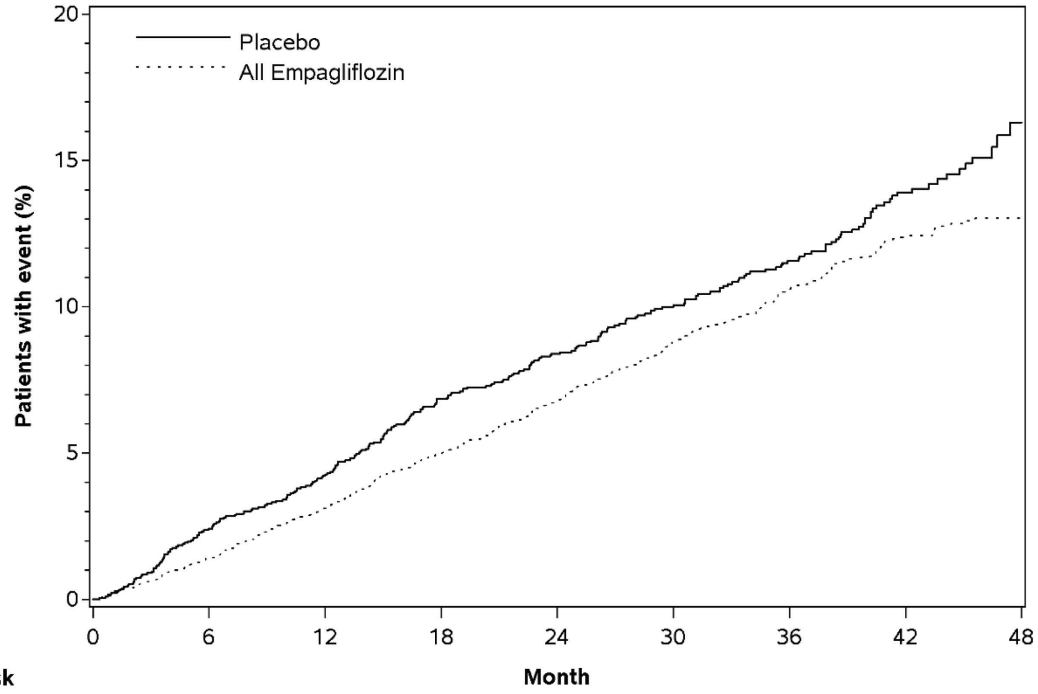
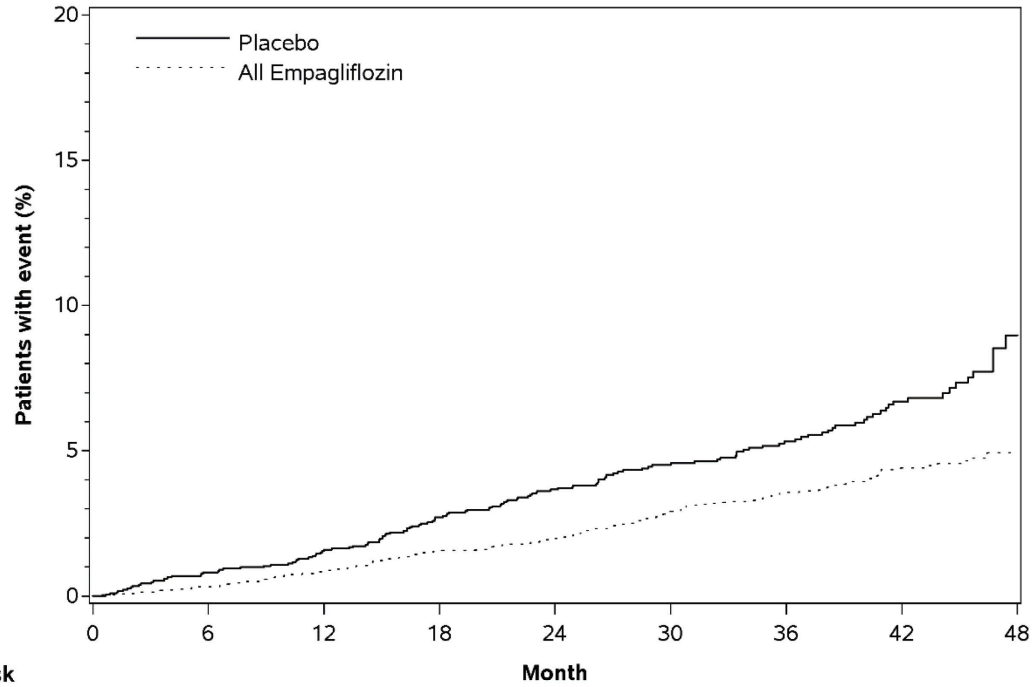
Figure 4 Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

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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).

14.3 Linagliptin Cardiovascular Safety Trial

The cardiovascular risk of linagliptin was evaluated in CARMELINA, a multi-national, 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 m^2. The mean eGFR was 55 mL/min/1.73 m^2 and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m^2), 47% of patients had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) and 15% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). 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, nonfatal myocardial infarction or nonfatal 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.

The results of CARMELINA, including the contribution of each component to the primary composite endpoint, are shown in Table 7. 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. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 6.

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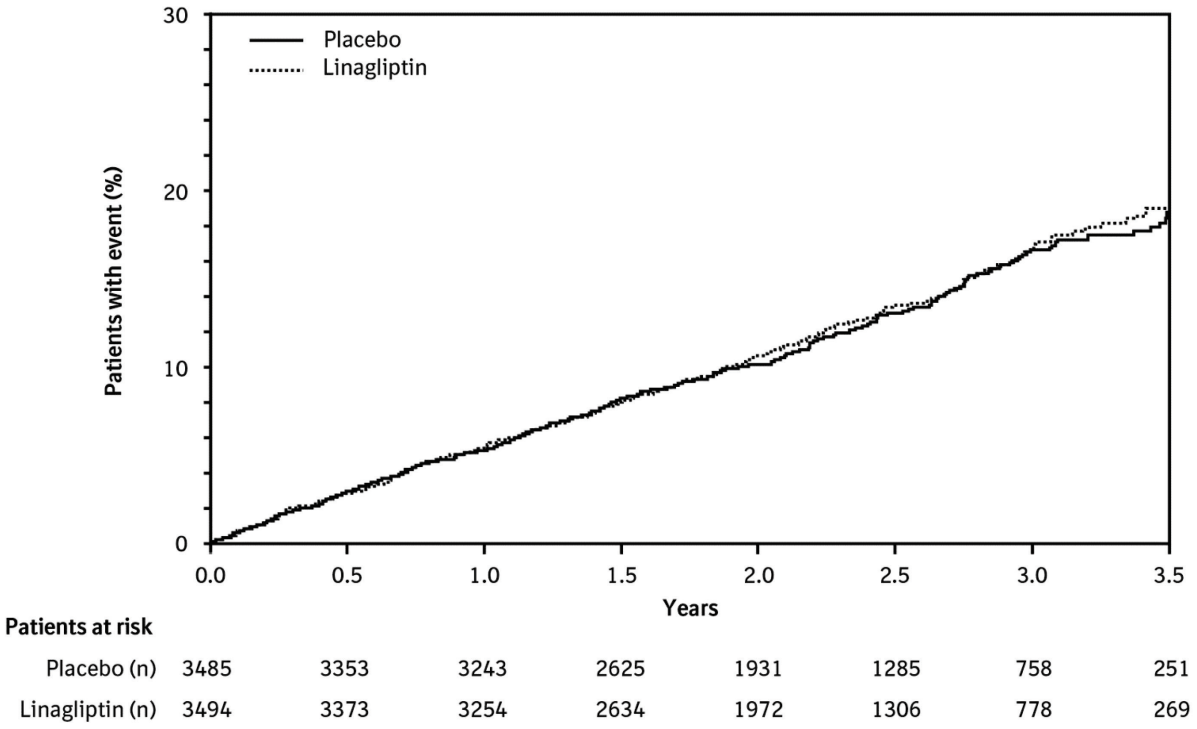
Table 7 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

	Linagliptin 5 mg n = 3494		Placebo n = 3485		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1000 PY[a]	Number of Subjects (%)	Incidence Rate per 1000 PY[a]	(95% CI)
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
CV death[b]	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
Non-fatal MI[b]	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
Non-fatal stroke[b]	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

[a]PY=patient years
[b]A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

Figure 6 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



16 HOW SUPPLIED/STORAGE AND HANDLING

GLYXAMBI (empagliflozin and linagliptin) tablets are available in 10 mg/5 mg and 25 mg/5 mg strengths as follows:

10 mg/5 mg tablets: 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".

Bottles of 30 (NDC 0597-0182-30)
Bottles of 90 (NDC 0597-0182-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0182-39), institutional pack.

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25 mg/5 mg tablets: 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".

Bottles of 30 (NDC 0597-0164-30)
Bottles of 90 (NDC 0597-0164-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0164-39), institutional pack.

If repackaging is required, dispense in a tight container as defined in USP.

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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 GLYXAMBI promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Heart Failure
Inform patients of the signs and symptoms of heart failure. Before initiating GLYXAMBI, 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 (5.2)]*.

Hypotension
Inform patients that hypotension may occur with GLYXAMBI 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 have adequate fluid intake.

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 GLYXAMBI and seek medical attention immediately *[see Warnings and Precautions (5.4)]*.

Acute Kidney Injury
Inform patients that acute kidney injury has been reported during use of empagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue GLYXAMBI use in those settings *[see Warnings and Precautions (5.5)]*.

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Monitoring of Renal Function
Inform patients that renal function should be assessed prior to initiation of GLYXAMBI and monitored periodically thereafter *[see Warnings and Precautions (5.5)]*.

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 (5.6)]*.

Hypoglycemia
Inform patients that the incidence of hypoglycemia is increased when empagliflozin, linagliptin, or GLYXAMBI is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

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 GLYXAMBI. 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 (5.8)]*.

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 (5.9)]*.

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 (5.9)]*.

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 GLYXAMBI. 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 GLYXAMBI and seek medical advice promptly *[see Warnings and Precautions (5.10)]*.

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 (5.12)]*.

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 (5.13)]*.

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

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Pregnancy
Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with GLYXAMBI *[see Use in Specific Populations (8.1)]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

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

Missed Dose
Instruct patients to take GLYXAMBI 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.

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MEDICATION GUIDE
GLYXAMBI® (glik-SAM-bee)
(empagliflozin and linagliptin)
Tablets

What is the most important information I should know about GLYXAMBI?
Serious side effects can happen to people taking GLYXAMBI, including:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.
  Before you start taking GLYXAMBI, tell your doctor if you have ever had:
  - inflammation of your pancreas (pancreatitis)
  - stones in your gallbladder (gallstones)
  - a history of alcoholism
  - high blood triglyceride levels

Stop taking GLYXAMBI and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- **Heart failure**. Heart failure means your heart does not pump blood well enough.
  Before you start taking GLYXAMBI, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:
  - increasing shortness of breath or trouble breathing, especially when you lie down
  - swelling or fluid retention, especially in the feet, ankles or legs
  - an unusually fast increase in weight
  - unusual tiredness

  These may be symptoms of heart failure.
- **Dehydration.** GLYXAMBI can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension).

You may be at higher risk of dehydration if you:

- have low blood pressure
- take medicines to lower your blood pressure, including diuretics (water pills)
- are on low sodium (salt) diet
- have kidney problems
- are 65 years of age or older

- **Vaginal yeast infection.** Women who take GLYXAMBI may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take GLYXAMBI may get a yeast infection of the skin around the penis. Men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may tell you to use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medicine and your symptoms do not go away.

What is GLYXAMBI?
GLYXAMBI is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and linagliptin (TRADJENTA). GLYXAMBI can be used:

- along with diet and exercise to lower blood sugar in adults with type 2 diabetes,
- in adults with type 2 diabetes who have known cardiovascular disease when both empagliflozin (JARDIANCE) and linagliptin (TRADJENTA) is appropriate and empagliflozin (JARDIANCE) is needed to reduce the risk of cardiovascular death.

- GLYXAMBI is not for people with type 1 diabetes.
- GLYXAMBI is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take GLYXAMBI.

It is not known if GLYXAMBI is safe and effective in children under 18 years of age.

Who should not take GLYXAMBI?
Do not take GLYXAMBI if you:

- have severe kidney problems or are on dialysis
- are allergic to linagliptin (TRADJENTA), empagliflozin (JARDIANCE) or any of the ingredients in GLYXAMBI. See

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the end of this Medication Guide for a complete list of ingredients in GLYXAMBI.
Symptoms of a serious allergic reaction to GLYXAMBI may include:

- skin rash, itching, flaking or peeling
- raised red patches on your skin (hives)
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- difficulty with swallowing or breathing

If you have any of these symptoms, stop taking GLYXAMBI and tell your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before taking GLYXAMBI?

Before you take GLYXAMBI, tell your doctor about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- have a history of infection of the vagina or penis
- have a history of urinary tract infection or problems with urination
- are going to have surgery. Your doctor may stop your GLYXAMBI before you have surgery. Talk to your doctor if you are having surgery about when to stop taking GLYXAMBI and when to start it again.
- are eating less, or there is a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking)
- are pregnant or plan to become pregnant. GLYXAMBI may harm your unborn baby. If you become pregnant while taking GLYXAMBI, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. GLYXAMBI may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking GLYXAMBI. Do not breastfeed while taking GLYXAMBI.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
GLYXAMBI may affect the way other medicines work, and other medicines may affect how GLYXAMBI works.

Especially tell your doctor if you take:

- insulin or other medicines that can lower your blood sugar
- diuretics (water pills)
- rifampin (Rifadin®, Rimactane®, Rifater®, Rifamate®), an antibiotic that is used to treat tuberculosis

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take GLYXAMBI?

- Take GLYXAMBI exactly as your doctor tells you to take it.
- Take GLYXAMBI 1 time each day in the morning, with or without food.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of GLYXAMBI at the same time.
- Your doctor may tell you to take GLYXAMBI along with other diabetes medicines. Low blood sugar can happen more often when GLYXAMBI is taken with certain other diabetes medicines. See "**What are the possible side effects of GLYXAMBI?**"
- If you take too much GLYXAMBI, call your doctor or local poison control center or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking GLYXAMBI.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- When taking GLYXAMBI, you may have sugar in your urine, which will show up on a urine test.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with GLYXAMBI.

What are the possible side effects of GLYXAMBI?

GLYXAMBI may cause serious side effects, including:

- See **"What is the most important information I should know about GLYXAMBI?"**
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes**, during treatment with empagliflozin, one of the medicines in GLYXAMBI. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with GLYXAMBI. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with GLYXAMBI even if your blood sugar is less than 250 mg/dL. Stop taking GLYXAMBI and call your doctor right away if you get any of the following symptoms**:
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with GLYXAMBI, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL**.**
- **Kidney problems.** Sudden kidney injury has happened to people taking GLYXAMBI. Talk to your doctor right away if you:
  - reduce the amount of food or liquid you drink for example, if you are sick or cannot eat or
  - start to lose liquids from your body for example, from vomiting, diarrhea or being in the sun too long
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking empagliflozin, one of the medicines in GLYXAMBI. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take GLYXAMBI with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take GLYXAMBI. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - irritability
  - hunger
  - fast heartbeat
  - confusion
  - shaking or feeling jittery
  - dizziness
  - sweating
- **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take empagliflozin, one of the medicines in GLYXAMBI. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in people who are taking GLYXAMBI. Symptoms may include:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking GLYXAMBI and tell your doctor or go to the nearest hospital emergency room right away.
- **Increased fats in your blood (cholesterol)**
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in GLYXAMBI, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in GLYXAMBI, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking GLYXAMBI.

The most common side effects of GLYXAMBI include:

- stuffy or runny nose and sore throat
- upper respiratory tract infection

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of GLYXAMBI. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GLYXAMBI?

- Store GLYXAMBI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep GLYXAMBI and all medicines out of the reach of children.

General information about the safe and effective use of GLYXAMBI.

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Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use GLYXAMBI for a condition for which it was not prescribed. Do not give GLYXAMBI to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about GLYXAMBI. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about GLYXAMBI that is written for health professionals.

For more information about GLYXAMBI including current prescribing information and Medication Guide, go to www.glyxambi.com, or scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in GLYXAMBI?

Active ingredients: empagliflozin and linagliptin

Inactive ingredients: mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc and magnesium stearate. The film coating contains the following inactive ingredients: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol.

10 mg/5 mg tablets also contain yellow ferric oxide.

25 mg/5 mg tablets also contain red ferric oxide.

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