GLYXAMBI- empagliflozin and linagliptin tablet, film coated
Boehringer Ingelheim Pharmaceuticals, Inc.

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 (5.4)	10/2025

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 (CV) death in adults with type 2 diabetes mellitus and established CV disease. (1)
Limitations of Use
- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. (1)
- Has not been studied in patients with a history of pancreatitis. (1)
- Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. (1)

DOSAGE AND ADMINISTRATION

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating. (2.1)
- The recommended dosage of GLYXAMBI is 10 mg empagliflozin and 5 mg linagliptin once daily, taken in the morning, with or without food. (2.2)
- Dosage may be increased to 25 mg empagliflozin and 5 mg linagliptin once daily. (2.2)
- Withhold GLYXAMBI for at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. (2.4)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI. (4)

WARNINGS AND PRECAUTIONS

- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider ketone monitoring in patients at risk of ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue GLYXAMBI if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- *Pancreatitis:* There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI. (5.2)
- *Volume Depletion:* Before initiating GLYXAMBI, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections:* Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated. Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for

necrotizing fasciitis and if suspected, discontinue GLYXAMBI, and promptly institute appropriate medical and/or surgical intervention. (5.4)
- *Hypoglycemia:* Consider lowering the dosage of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating GLYXAMBI. (5.5)
- *Lower Limb Amputation:* Monitor patients for infections or ulcers of lower limbs, and institute appropriate treatment. (5.6)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema, and exfoliative skin conditions) have occurred with empagliflozin and linagliptin. If hypersensitivity reactions occur, discontinue GLYXAMBI, treat promptly, and monitor until signs and symptoms resolve. (5.7)
- *Arthralgia:* Severe and disabling arthralgia has been reported in patients taking linagliptin. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.8)
- *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. (5.9)
- *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. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (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 FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

See full prescribing information for information on drug interactions and interference of GLYXAMBI with laboratory tests. (7)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* 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. (8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2026

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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 (CV) death in adults with type 2 diabetes mellitus and established CV disease *[see Clinical Studies (14.2)]*.

Limitations of Use

GLYXAMBI is not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1)]*.

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 (5.2)].*

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

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of GLYXAMBI

- Assess renal function before initiating GLYXAMBI and as clinically indicated *[see Warnings and Precautions (5.3)]*.
- Assess volume status. In patients with volume depletion, correct this condition before initiating GLYXAMBI *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage and Administration

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

2.3 Dosage Recommendations in Patients with Renal Impairment

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

2.4 Temporary Interruption for Surgery

Withhold GLYXAMBI for at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume GLYXAMBI when the patient is clinically stable and has resumed oral intake *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)].*

2.5 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.

3 DOSAGE FORMS AND STRENGTHS

GLYXAMBI tablets available as:

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

company symbol; the other side is debossed with "10/5".
- 25 mg empagliflozin/5 mg linagliptin are pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

4 CONTRAINDICATIONS

GLYXAMBI is contraindicated in patients:
- with a hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (5.7) and Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, empagliflozin, a component of GLYXAMBI, significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose co-transporter 2 (SGLT2) inhibitors compared to patients who received placebo and fatal ketoacidosis has occurred with empagliflozin. GLYXAMBI is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including GLYXAMBI.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing GLYXAMBI *[see Clinical Pharmacology (12.2)];* however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue GLYXAMBI, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting GLYXAMBI.

Withhold GLYXAMBI, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume GLYXAMBI when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.4)].*

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

5.2 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.

5.3 Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (6.1)].* There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating GLYXAMBI in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating GLYXAMBI. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.4 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Empagliflozin increases urinary glucose excretion *[see Clinical Pharmacology (12.2)]* and increases the risk of genitourinary infections including urinary tract infections and genital mycotic infections in both male and female patients *[see Adverse Reactions (6.1)].*

Serious genitourinary infections, including urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier's gangrene, a rare life-threatening infection requiring urgent surgical intervention), have occurred in patients with or without diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin *[see Adverse Reactions (6.2)].* Cases have required hospitalization. In patients with Fournier's gangrene, serious outcomes have included multiple surgeries and death. GLYXAMBI is only indicated for use in patients with type 2 diabetes mellitus.

Patients with a history of chronic or recurrent genitourinary infections are more likely to

develop genitourinary infections when using GLYXAMBI. Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated.

Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis. If suspected, discontinue GLYXAMBI and promptly institute appropriate medical and/or surgical intervention.

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

5.6 Lower Limb Amputation

In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95 % CI) (0.81, 1.36).

In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg treatment arms, respectively. Amputation of the toe and mid-foot were most frequent (21 out of 28 empagliflozin 10 mg treated patients with lower limb amputations), and some involving above and below the knee. Some patients had multiple amputations. GLYXAMBI is not indicated for the treatment of chronic kidney disease.

Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot, peripheral artery disease (including previous amputation) or diabetes.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving GLYXAMBI for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

5.7 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose.

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

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

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 hypersensitivity to linagliptin, empagliflozin or any of the excipients in GLYXAMBI *[see Contraindications (4)]*.

5.8 Severe and Disabling Arthralgia

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

5.9 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.

5.10 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.

6 ADVERSE REACTIONS

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

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[see Warnings and Precautions (5.3)]*

- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.8)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.9)]*
- Heart Failure *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Empagliflozin and Linagliptin

The safety of concomitantly administered empagliflozin (daily dosage 10 mg or 25 mg) and linagliptin (daily dosage 5 mg) has been evaluated in a total of 1,363 patients with type 2 diabetes mellitus 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 trials are shown in Table 1.

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

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

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

Empagliflozin

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

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

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Events related to volume

depletion (hypotension and syncope) were reported in 3 patients (1.1%) treated with GLYXAMBI plus metformin.

Linagliptin

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

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

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

Other Adverse Reactions

Hypoglycemia

Empagliflozin and Linagliptin

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

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

Add-on to Metformin (52 weeks)	**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

Empagliflozin

- *Genital Mycotic Infections*: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 mg or 25 mg.
  Genital mycotic infections occurred more frequently in female than male patients. Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).
- *Urinary Tract Infections:* In the pool of five placebo-controlled clinical trials, the

incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared to placebo. Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.
Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations (8.5)]*.

- *Lower Limb Amputations:* Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95% CI) (0.81, 1.36). In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg treatment arms, respectively. GLYXAMBI is not indicated for the treatment of chronic kidney disease.

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin or Linagliptin

Empagliflozin and Linagliptin

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

Empagliflozin

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

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: Median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Linagliptin

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

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

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

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

The clinical significance of elevations in lipase and amylase with linagliptin is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of linagliptin and empagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (1)]*, constipation, mouth ulceration, stomatitis

Immune System Disorders: Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions

Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis

Metabolism and Nutrition Disorders: Ketoacidosis

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis, severe and disabling arthralgia

Renal and Urinary Disorders: Acute kidney injury

Skin and Subcutaneous Tissue Disorders: Bullous pemphigoid, skin reactions (e.g., rash, urticaria)

7 DRUG INTERACTIONS

Table 3 describes clinically relevant interactions with GLYXAMBI.

Table 3 Clinically Relevant Interactions with GLYXAMBI

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Intervention	Before initiating GLYXAMBI, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating GLYXAMBI. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when GLYXAMBI is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of GLYXAMBI with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during GLYXAMBI initiation and dosage changes.
Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

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

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

The combined components administered during the period of organogenesis were not teratogenic in rats up to and including a combined dose of 700 mg/kg/day empagliflozin and 140 mg/kg/day linagliptin, which is 253- and 353-times the clinical exposure. A pre- and postnatal development study was not conducted with the combined components of 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 empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

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

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

8.2 Lactation

Risk Summary

There is limited 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 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

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

8.5 Geriatric Use

GLYXAMBI

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

Empagliflozin

In empagliflozin type 2 diabetes mellitus trials, 2,721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these

trials, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

Linagliptin

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

8.6 Renal Impairment

Empagliflozin

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Efficacy and safety trials with empagliflozin for glycemic control and the EMPA-REG OUTCOME trial did not enroll patients with ESRD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. *[see Indications and Usage (1)]*.

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, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

11 DESCRIPTION

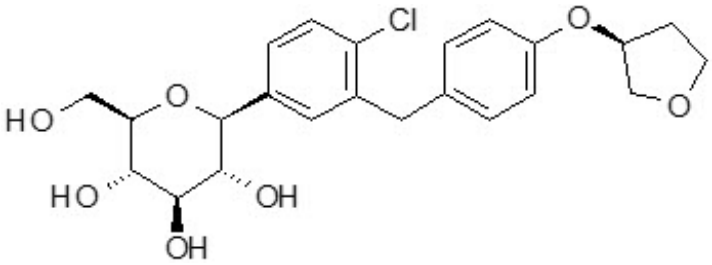
GLYXAMBI tablets for oral use contain: empagliflozin and linagliptin.

Empagliflozin

Empagliflozin is an inhibitor of the SGLT2.

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

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



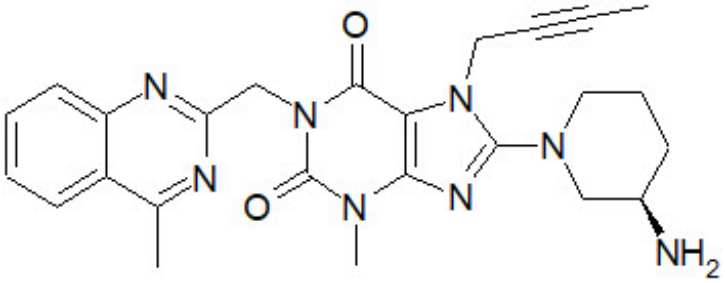
Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Linagliptin

Linagliptin is an inhibitor of the 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 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: copovidone, corn starch, crospovidone, magnesium stearate, mannitol, pregelatinized starch, and talc. Coating: ferric oxide yellow (10 mg/5 mg) or ferric oxide red (25 mg/5 mg), hypromellose, mannitol, polyethylene glycol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GLYXAMBI

GLYXAMBI contains: empagliflozin, a SGLT2 inhibitor, and linagliptin, a DPP-4 inhibitor.

Empagliflozin

Empagliflozin is an inhibitor of SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By

inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Linagliptin

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

12.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

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

Cardiac Electrophysiology

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

100 mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

GLYXAMBI

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.

Empagliflozin

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

Absorption

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

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Elimination

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

Metabolism

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

Excretion

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

Linagliptin

Absorption

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Linagliptin: Based on the population PK analysis, age, body mass index (BMI), gender and race do not have a clinically meaningful effect on pharmacokinetics of linagliptin *[see Use in Specific Populations (8.5)]*.

Patients with Renal Impairment

GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin

after administration of GLYXAMBI in renally impaired patients have not been performed.

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

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

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

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

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

Patients with Hepatic Impairment

GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in hepatically impaired patients have not been performed.

Empagliflozin: In patients with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Drug Interaction Studies

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

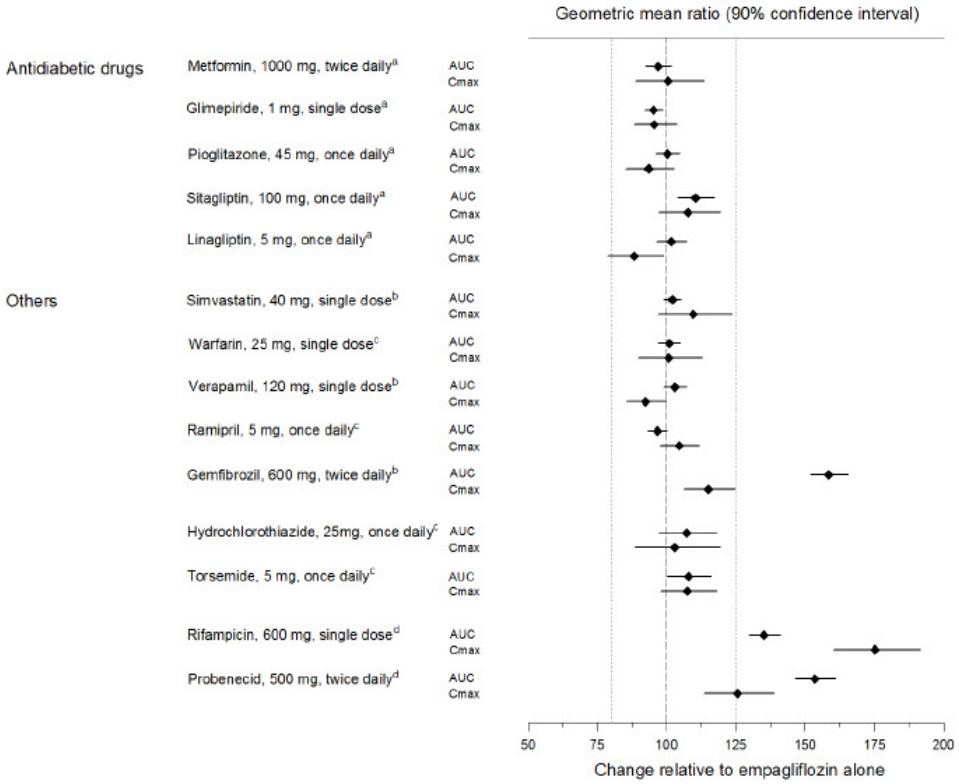
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9 and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes mellitus (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

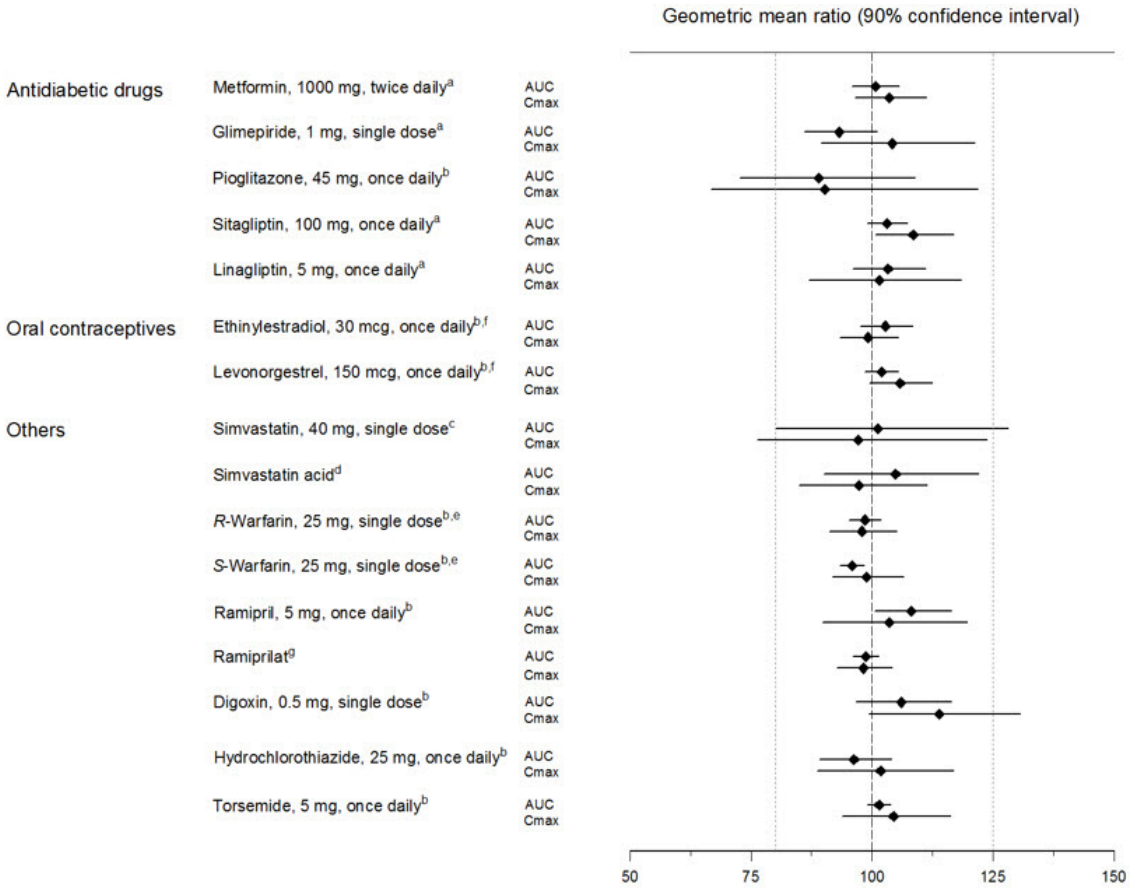
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

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

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



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

Linagliptin

In vitro Assessment of Drug Interactions

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

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

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations *[see Drug Interactions (7)]*. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 4 describes the effect of coadministered drugs on systemic exposure of linagliptin.

Table 4 Effect of Coadministered Drugs on Systemic Exposure of

Linagliptin

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

[a]Multiple dose (steady-state) unless otherwise noted
[b]For information regarding clinical recommendations *[see Drug Interactions (7)]*.
[c]Single dose
[d]AUC = AUC (0 to 24 hours) for single dose treatments and AUC = AUC (TAU) for multiple-dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 5 describes the effect of linagliptin on systemic exposure of coadministered drugs.

Table 5 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

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

Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol	1.01	1.08
			levonorgestrel	1.09	1.13

[a]Multiple dose (steady-state) unless otherwise noted
[b]Single dose
[c]AUC = AUC (INF) for single dose treatments and AUC = AUC (TAU) for multiple dose treatments
[d]AUC = AUC (0-168) and $C_{max} = E_{max}$ for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GLYXAMBI

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

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Linagliptin

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

based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

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

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

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Patients with Type 2 Diabetes Mellitus

Add-on Combination Therapy with Metformin

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

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 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 dosage combination tablet.

At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin (see Table 6, Figure 3). Treatment with 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.

Table 6 Glycemic Parameters at 24 Weeks in a Trial 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]	--	--	--

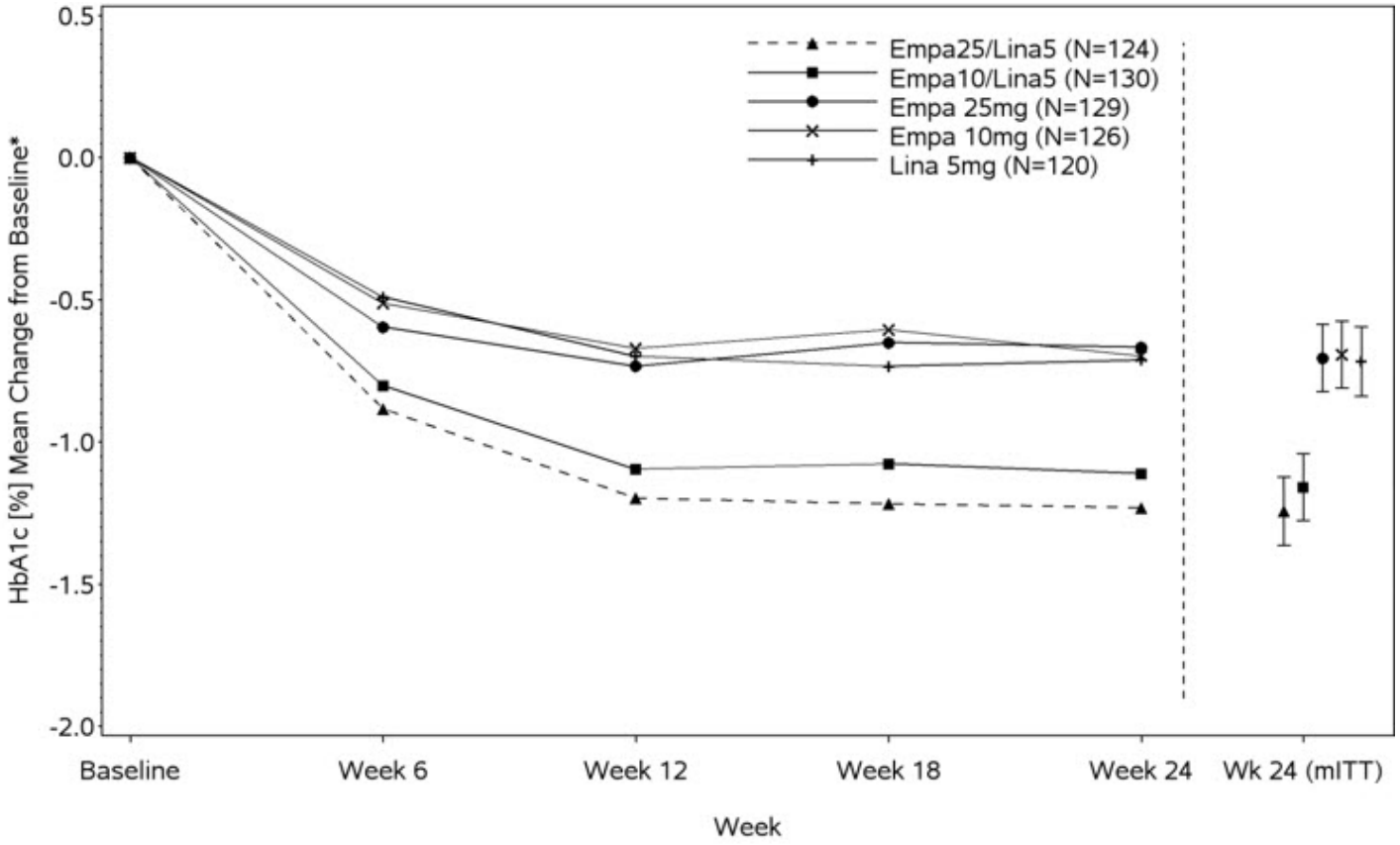
[a]Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.

[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

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 Outcomes in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

EMPA-REG OUTCOME was a multicenter, multinational, randomized, double-blind parallel group trial that 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 mellitus and atherosclerotic CV disease. Concomitant antidiabetic medications were 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 7,020 patients were treated (empagliflozin 10 mg = 2,345; empagliflozin 25 mg = 2,342; placebo = 2,333) and followed for a median of 3.1 years. Approximately 72% of the trial population was White, 22% was Asian, and 5% was Black or African American. The mean age was 63 years and approximately 72% were male.

All patients in the trial 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 mellitus 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%).

All patients had established atherosclerotic CV 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 CV death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg dosages 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.

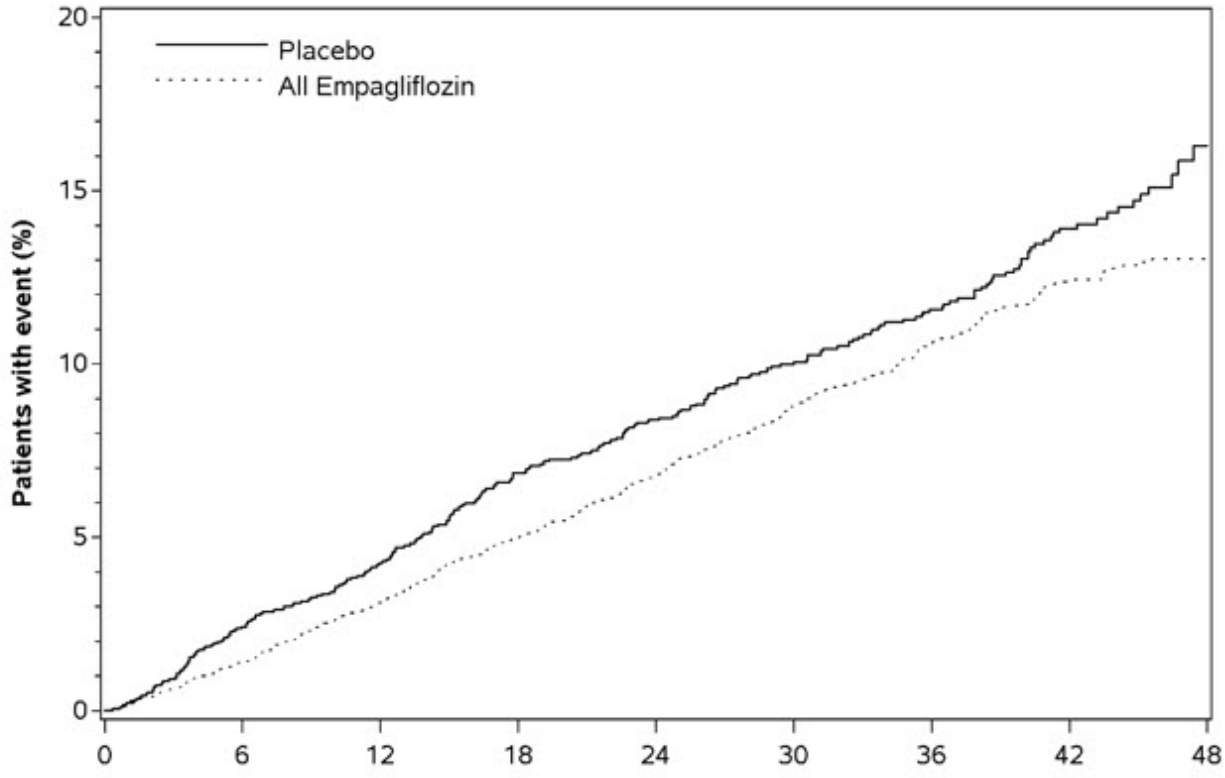
Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI: 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of CV death in subjects randomized to empagliflozin (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 7 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin dosages were consistent with results for the combined dosage groups.

Table 7 Treatment Effect for the Primary Composite Endpoint and its Components[a]

	Placebo N=2,333	**Empagliflozin N=4,687**	**Hazard ratio vs placebo (95% CI)**
Composite of CV 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)
CV 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 trial drug)
[b]p-value for superiority (2-sided) 0.04
[c]Total number of events

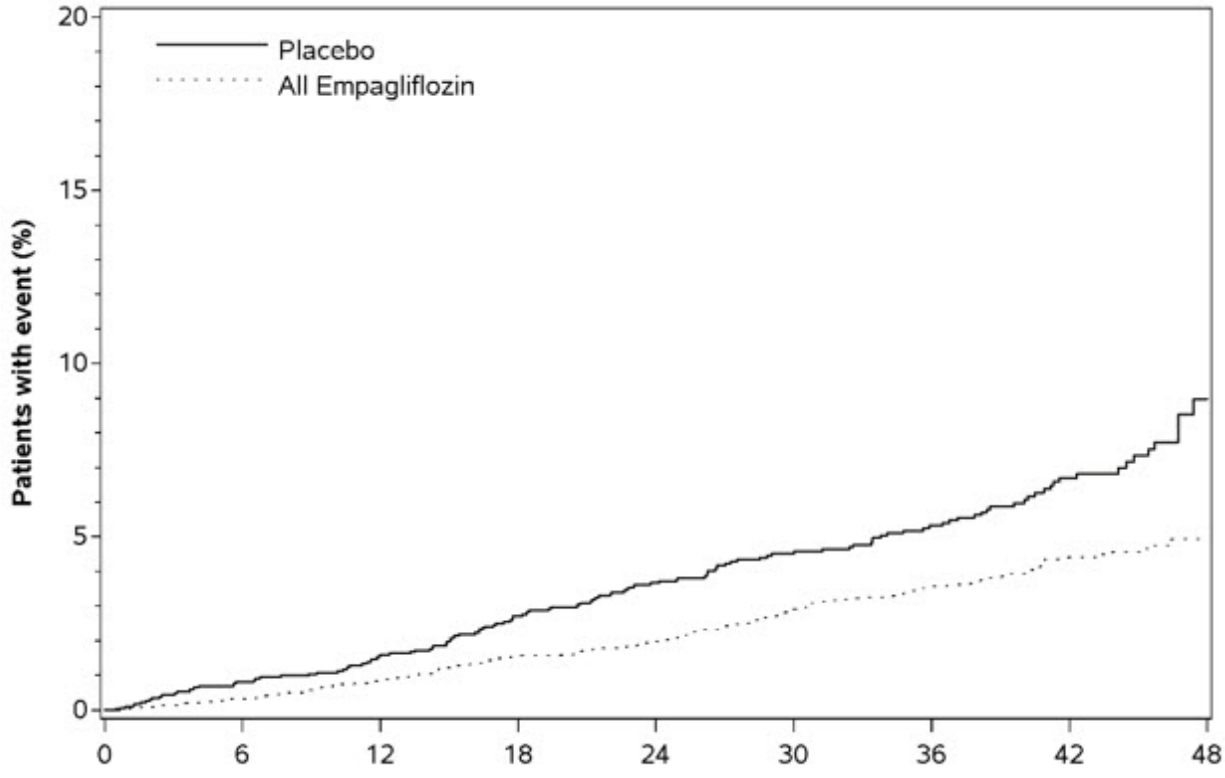
Figure 4 Estimated Cumulative Incidence of First MACE



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 CV 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

The efficacy of empagliflozin on CV 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 CV deaths. The non-CV 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 Trials in Patients with Type 2 Diabetes Mellitus

CARMELINA

The CV risk of linagliptin was evaluated in CARMELINA, a multinational, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3,494) to placebo (N=3,485) 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 mellitus and other CV 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 mellitus, 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% White, 9% Asian, 6% Black or African American and 36% were of Hispanic or Latino ethnicity. 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 CV death, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 434 patients on linagliptin and 420 patients on placebo experienced MACE. The incidence rate of MACE in both treatment arms: 56.3 MACE per 1,000 patient-years on placebo vs. 57.7 MACE per 1,000 patient-years on linagliptin. The estimated hazard ratio for MACE associated with linagliptin relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3.

CAROLINA

The CV risk of linagliptin was evaluated in CAROLINA, a multi-center, multinational,

randomized, double-blind parallel group trial comparing linagliptin (N=3,023) to glimepiride (N=3,010) in adult patients with type 2 diabetes mellitus and a history of established CV disease and/or multiple CV risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and glimepiride when these were added to standard of care treatments for diabetes mellitus and other CV risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

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

At baseline the mean age was 64 years and the population was 60% male, 73% White, 18% Asian, 5% Black or African American, and 17% were of Hispanic or Latino ethnicity. The mean HbA1c was 7.15% and mean duration of type 2 diabetes mellitus was 7.6 years. The trial population included 34% patients ≥70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 77 mL/min/1.73 m^2. Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included CV death, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 356 patients on linagliptin and 362 patients on glimepiride experienced MACE. The incidence rate of MACE in both treatment arms: 20.7 MACE per 1,000 patient-years on linagliptin vs. 21.2 MACE per 1,000 patient-years on glimepiride. The estimated hazard ratio for MACE associated with linagliptin relative to glimepiride was 0.98 with a 95% confidence interval of (0.84, 1.14). The upper bound of this confidence interval, 1.14, excluded the risk margin of 1.3.

16 HOW SUPPLIED/STORAGE AND HANDLING

GLYXAMBI tablets are available 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 × 10) (NDC 0597-0182-39), institutional pack.

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 × 10) (NDC 0597-0164-39), institutional pack.

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

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that GLYXAMBI can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed insulin doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue GLYXAMBI and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

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 healthcare provider if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

Volume Depletion

Inform patients that symptomatic 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 maintain adequate fluid intake.

Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Counsel patients that genitourinary infections may occur when taking empagliflozin, a component of GLYXAMBI, and may become serious. Educate them on the symptoms and advise them to seek medical advice if symptoms occur. Specifically, advise 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 (5.4)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the risk of hypoglycemia is increased when GLYXAMBI is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin *[see Warnings and Precautions (5.5)]*.

Lower Limb Amputation

Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions (5.6)]*.

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 (5.7)]*.

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 (5.8)]*.

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 (5.9)].*

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 (5.10)]*.

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking GLYXAMBI *[see Drug Interactions (7)]*.

Pregnancy

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

Lactation

Advise patients that breastfeeding is not recommended during treatment with 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 *[see Dosage and Administration (2.5)]*.

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MEDICATION GUIDE
GLYXAMBI® (glik-SAM-bee)
(empagliflozin and linagliptin tablets)
for oral use

What is the most important information I should know about GLYXAMBI?
GLYXAMBI can cause serious side effects, including:

- **Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 and other ketoacidosis.** GLYXAMBI can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who: are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet), take less than the usual amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery. Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your healthcare provider may ask you to periodically check ketones in your urine or blood.
  Stop taking GLYXAMBI and call your healthcare provider or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL:

- nausea
- vomiting
- stomach-area (abdominal) pain
- tiredness
- trouble breathing
- ketones in your urine or blood

- **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 healthcare provider if you have ever had:
  - inflammation of your pancreas (pancreatitis)
  - a history of alcoholism
  - stones in your gallbladder (gallstones)
  - high blood triglyceride levels

  Stop taking GLYXAMBI and call your healthcare provider 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.
- **Dehydration. GLYXAMBI can cause some people to become dehydrated (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). There have been reports of sudden worsening of kidney function in people who are taking GLYXAMBI.** You may be at higher risk of dehydration if you:
  - take medicines to lower your blood pressure, including diuretics (water pills)
  - are on a low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older

  Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or you cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

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 (glucose) in adults with type 2 diabetes,
- in adults with type 2 diabetes who have known cardiovascular disease when empagliflozin (JARDIANCE), one of the medicines in GLYXAMBI, is needed to reduce the risk of cardiovascular death.

- GLYXAMBI is not for use to lower blood sugar (glucose) in people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in 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.
- GLYXAMBI is not for use to lower blood sugar (glucose) in people with type 2

diabetes who have severe kidney problems, because it may not work.
- It is not known if GLYXAMBI is safe and effective in children.

Who should not take GLYXAMBI?
Do not take GLYXAMBI if you:
- are allergic to linagliptin (TRADJENTA), empagliflozin (JARDIANCE) or any of the ingredients in GLYXAMBI. See 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 call your healthcare provider right away or go to the nearest hospital emergency room.

What should I tell my healthcare provider before taking GLYXAMBI?
Before taking GLYXAMBI, tell your healthcare provider about all of your medical conditions, including if you:
- have type 1 diabetes or have had diabetic ketoacidosis.
- have a decrease in your insulin dose.
- have a serious infection.
- have a history of infection of the vagina or penis.
- have a history of amputation.
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your healthcare provider may change your diet or your dose.
- are going to have surgery. Your healthcare provider may stop your GLYXAMBI before you have surgery. Talk to your healthcare provider 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.
- are dehydrated.
- 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).
- have ever had an allergic reaction to GLYXAMBI.
- are pregnant or plan to become pregnant. GLYXAMBI may harm your unborn baby. If you become pregnant while taking GLYXAMBI, tell your healthcare provider as soon as possible. Talk with your healthcare provider 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 healthcare provider about the best way to feed your baby if you are taking GLYXAMBI. Do not breastfeed while taking GLYXAMBI.

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

How should I take GLYXAMBI?

- Take GLYXAMBI exactly as your healthcare provider tells you to take it.
- Take GLYXAMBI by mouth 1 time each day in the morning, with or without food.
- Your healthcare provider will tell you how much GLYXAMBI to take and when to take it. Your healthcare provider may change your dose if needed.
- Your healthcare provider 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 miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take two doses of GLYXAMBI at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- If you take too much GLYXAMBI, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.
- When taking GLYXAMBI, you may have sugar in your urine, which will show up on a urine test.
- 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 you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- Your healthcare provider may do certain blood tests before you start GLYXAMBI and during treatment as needed.

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?"**
- **Genital and urinary tract infections.** Empagliflozin, one of the medicines in GLYXAMBI, can cause serious infections in your genital area or urinary tract that could require hospitalization. **A rare but serious bacterial infection called necrotizing fasciitis can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum).** This infection may require hospitalization, multiple surgeries, and could 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)

  Also tell your healthcare provider if you have any of these signs or symptoms of urinary tract infections or yeast infections:

  - **Urinary tract infection:**

- burning feeling when you urinate
- need to urinate often or right away
- pain in the lower part of your stomach (pelvis)
- blood in your urine

You may also have a fever, back pain, nausea, or vomiting.

- **Vaginal yeast infection:**
  - vaginal odor
  - white or yellowish vaginal discharge (may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the skin around the penis (balanitis or balanoposthitis):** If you are uncircumcised, swelling may make it difficult to pull back the skin around the tip of your penis. Other symptoms include:
  - redness, itching, or swelling of the penis
  - bad smelling discharge from the penis
  - rash on the penis
  - pain in the skin around the penis

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection. They may suggest you use an over-the-counter antifungal medicine. Contact your healthcare provider right away if your symptoms do not improve after using an over-the-counter antifungal medicine.

- **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

- **Amputations. SGLT2 inhibitors may increase your risk of lower limb amputations.**
  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have had blocked or narrowed blood vessels, usually in your leg
  - have had diabetic foot infection, ulcers or sores

  Call your healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Talk to your healthcare provider about proper foot care.
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking GLYXAMBI and call your healthcare provider right away or go to the nearest hospital emergency room. See **"Who should not take GLYXAMBI?".**
- **Joint pain.** Some people who take linagliptin, one of the medicines in GLYXAMBI, may develop joint pain that can be severe. Call your healthcare provider 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 healthcare provider right away if you

develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking GLYXAMBI.

- **Heart failure.** Heart failure means your heart does not pump blood well enough. **Before you start taking GLYXAMBI,** tell your healthcare provider if you have ever had heart failure or have problems with your kidneys. Contact your healthcare provider 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.

The most common side effects of GLYXAMBI include:

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

Tell your healthcare provider 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 healthcare provider 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.
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.
You can ask your pharmacist or healthcare provider for information about GLYXAMBI that is written for health professionals.

What are the ingredients in GLYXAMBI?
Active ingredients: empagliflozin and linagliptin
Inactive ingredients: copovidone, corn starch, crospovidone, magnesium stearate, mannitol, pregelatinized starch, and talc. The film coating contains the following inactive ingredients: hypromellose, mannitol, polyethylene glycol, talc, and titanium dioxide.
10 mg/5 mg tablets also contain ferric oxide yellow.
25 mg/5 mg tablets also contain ferric oxide red.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: January 2026

PRINCIPAL DISPLAY PANEL - 10 mg/5 mg Tablet Bottle Label

NDC 0597-0182-90

Glyxambi®

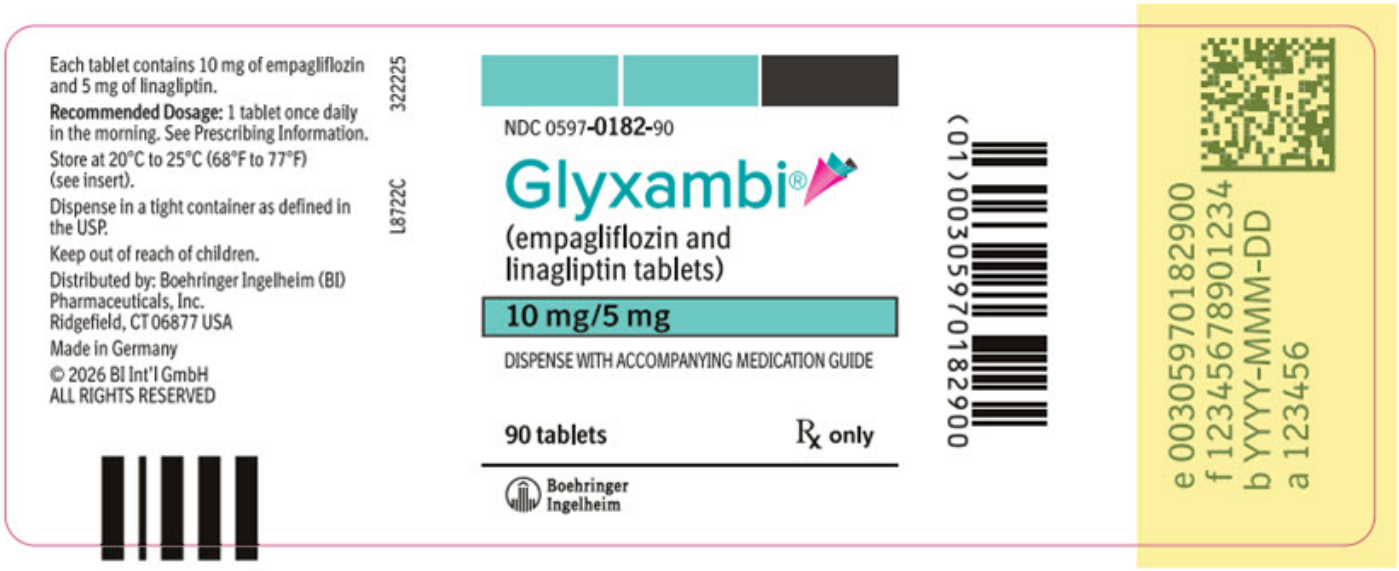
(empagliflozin and
linagliptin tablets)

10 mg/5 mg

DISPENSE WITH ACCOMPANYING MEDICATION GUIDE

90 tablets
Rx only

Boehringer
Ingelheim



PRINCIPAL DISPLAY PANEL - 25 mg/5 mg Tablet Bottle Label

NDC 0597-0164-90

Glyxambi®

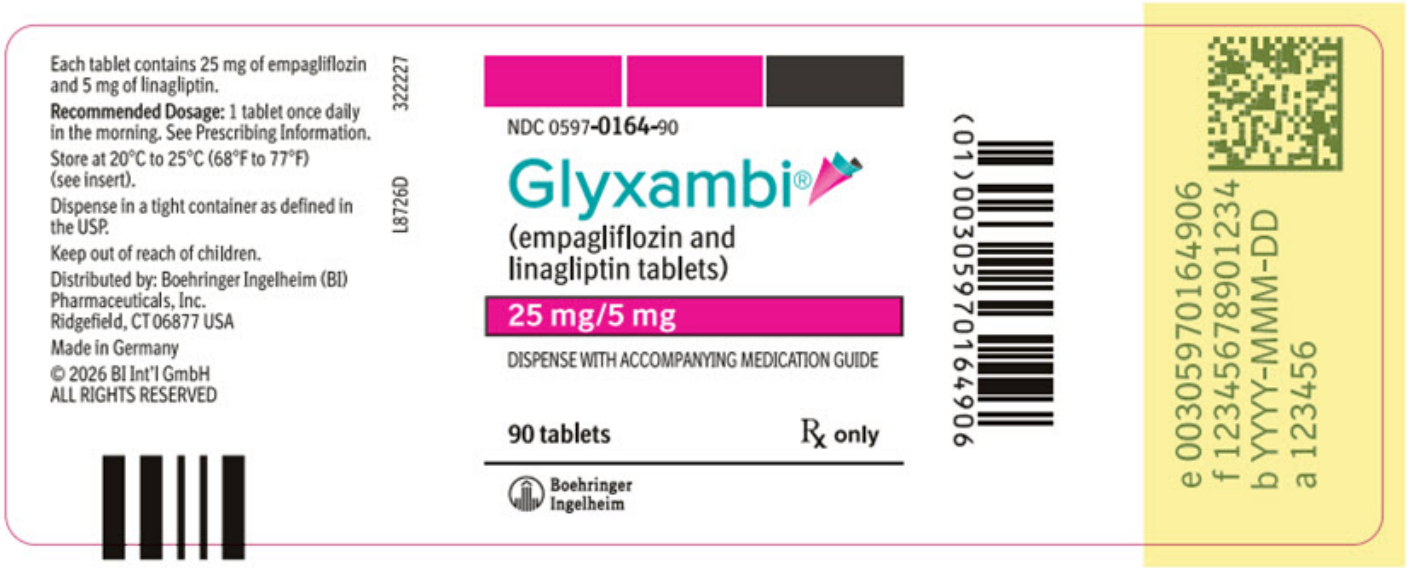
(empagliflozin and
linagliptin tablets)

25 mg/5 mg

DISPENSE WITH ACCOMPANYING MEDICATION GUIDE

90 tablets
Rx only

Boehringer
Ingelheim



GLYXAMBI

empagliflozin and linagliptin tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0182
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	10 mg
LINAGLIPTIN (UNII: 3X29ZEJ4R2) (LINAGLIPTIN - UNII:3X29ZEJ4R2)	LINAGLIPTIN	5 mg

Product Characteristics			
Color	YELLOW (pale yellow)	**Score**	no score

Shape	TRIANGLE	**Size**	8mm
Flavor		**Imprint Code**	10;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0182-70	7 in 1 CARTON	01/30/2015	05/01/2017
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:0597-0182-07	1 in 1 CARTON	01/30/2015	01/31/2026
2		7 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:0597-0182-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2015	09/30/2016
4	NDC:0597-0182-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2015	
5	NDC:0597-0182-39	30 in 1 CARTON	01/30/2015	
5		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
6	NDC:0597-0182-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206073	01/30/2015	

GLYXAMBI

empagliflozin and linagliptin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0164
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	25 mg
LINAGLIPTIN (UNII: 3X29ZEJ4R2) (LINAGLIPTIN - UNII:3X29ZEJ4R2)	LINAGLIPTIN	5 mg

Product Characteristics

Color	PINK (pale pink)	**Score**	no score

Shape	TRIANGLE	**Size**	8mm
Flavor		**Imprint Code**	25;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0164-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2015	
2	NDC:0597-0164-39	30 in 1 CARTON	01/30/2015	
2		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:0597-0164-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2015	
4	NDC:0597-0164-70	7 in 1 CARTON	01/30/2015	05/01/2017
4		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
5	NDC:0597-0164-07	1 in 1 CARTON	01/30/2015	10/31/2025
5		7 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206073	01/30/2015	

Labeler - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

Registrant - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Pharma GmbH and Co. KG		551147440	MANUFACTURE(0597-0164, 0597-0182) , API MANUFACTURE(0597-0164, 0597-0182) , PACK(0597-0164, 0597-0182) , LABEL(0597-0164, 0597-0182)

Establishment

Name	Address	ID/FEI	Business Operations
Sixarp, LLC		016329513	PACK(0597-0164, 0597-0182) , LABEL(0597-0164, 0597-0182)

Establishment

Name	Address	ID/FEI	Business Operations
Rottendorf Pharma GmbH		315974691	MANUFACTURE(0597-0164, 0597-0182) , PACK(0597-0164, 0597-0182) , LABEL(0597-0164, 0597-0182)