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----------

Indications and Usage (1)	6/2021
Dosage and Administration (2.1, 2.3)	6/2021
Contraindications (4)	6/2021
Warnings and Precautions (5.2, 5.3)	6/2021

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

GLYXAMBI is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitations of Use

- Not recommended 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 (2.1)
- The recommended dose of GLYXAMBI is 10 mg empagliflozin and 5 mg linagliptin once daily, taken in the morning, with or without food (2.2)
- Dose may be increased to 25 mg empagliflozin and 5 mg linagliptin once daily (2.2)

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

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

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

- Patients on dialysis (4)
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI (4, 5.8)

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

- *Pancreatitis:* There have been reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI. (5.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue GLYXAMBI, evaluate and treat promptly. Before initiating GLYXAMBI, consider risk factors for ketoacidosis. Patients on GLYXAMBI may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *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, 6.1)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.4)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating GLYXAMBI (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.6)
- *Genital Mycotic Infections:* Monitor and treat as appropriate (5.7)
- *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. (5.8)
- *Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.9)
- *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. (5.10)
- *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. (5.11)

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

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

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

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

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- *Lactation:* GLYXAMBI is not recommended when breastfeeding (8.2)
- *Pediatric Patients*: Safety and effectiveness of GLYXAMBI in pediatric patients have not been established (8.4)
- *Geriatric Patients:* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.3, 8.5, 8.6)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (2.1, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLYXAMBI is a combination of empagliflozin and linagliptin indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14)]*.

Limitations of Use

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

GLYXAMBI has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using GLYXAMBI *[see Warnings and Precautions (5.1)]*.

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 Prior to Initiation of GLYXAMBI

- Assess renal function before initiating GLYXAMBI and as clinically indicated *[see Warnings and Precautions (5.3)]*.
- 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

The recommended dose 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 and contraindicated in patients on dialysis *[see Indications and Usage (1), Contraindications (4), Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

GLYXAMBI tablets are a combination of empagliflozin and linagliptin available as:

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial *[see Clinical Studies (14)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

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

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. GLYXAMBI is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

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

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

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

For patients who undergo scheduled surgery, consider temporarily discontinuing GLYXAMBI for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

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

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

5.3 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 Urosepsis and Pyelonephritis

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

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

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

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

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

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

5.7 Genital Mycotic Infections

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

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