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 (5.3, 5.5)	12/2015
Warnings and Precautions (5.10)	8/2015

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

GLYXAMBI is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate. (1)

Limitations of use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.1)
- Has not been studied in patients with a history of pancreatitis (1.1)

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

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

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

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

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

- Severe renal impairment, end-stage renal disease, or dialysis (4)
- History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)
- History of serious hypersensitivity reaction to empagliflozin (4)

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

- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI. (5.1)
- *Hypotension:* Before initiating GLYXAMBI assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.2)
- *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. (5.3)
- *Impairment in Renal Function:* Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating GLYXAMBI. (5.6)
- *Genital Mycotic Infections:* Monitor and treat as appropriate (5.7)
- *Hypersensitivity:* There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of GLYXAMBI) including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue GLYXAMBI, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.8)
- *Increased LDL-C:* Monitor and treat as appropriate (5.9)
- *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. (5.10)
- *Macrovascular Outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLYXAMBI or any other antidiabetic drug. (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 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- *Pregnancy:* There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing Mothers:* Discontinue GLYXAMBI or discontinue nursing (8.3)
- *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 (5.2, 5.4, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLYXAMBI tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate *[see Clinical Studies (14)]*.

1.1 Limitations of Use

GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

In patients with volume depletion, correcting this condition prior to initiation of GLYXAMBI is recommended *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.

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

2.2 Patients with Renal Impairment

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

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

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

GLYXAMBI should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.2, 5.4), and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

GLYXAMBI is contraindicated in patients with:

- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.
- A history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity *[see Warnings and Precautions (5.8) and Adverse Reactions (6)]*.
- History of serious hypersensitivity reaction to empagliflozin.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking 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 Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating GLYXAMBI, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. 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 due to illness or 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. In patients treated with GLYXAMBI consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Impairment in Renal Function

Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients *[see Use in Specific Populations (8.5, 8.6)]*. Renal function should be evaluated prior to initiating GLYXAMBI and periodically thereafter.

5.5 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)]*.

5.6 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.

5.7 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 mycotic genital infections. Monitor and treat as appropriate.

5.8 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of GLYXAMBI). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue GLYXAMBI, assess for other potential causes for the event, and institute alternative treatment for diabetes.

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.

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

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

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