BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/07/15**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE: 5/16/19
	ARCHIVE DATE:

GLYXAMBI ® (empagliflozin-linagliptin) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Glyxambi (empagliflozin and linagliptin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 18 years of age or older
  2. A confirmed diagnosis of type 2 diabetes mellitus
  3. Inadequate glycemic control with a hemoglobin A1c greater than 7%
  4. Failed to obtain adequate glycemic control with adherence to both diabetic diet and exercise program (documentation of adherence must be submitted with the request)
  5. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use Metformin
  6. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use a combination of preferred SGLT2 inhibitor (Farxiga, Invokana, or Jardiance) plus a preferred DPP-4 inhibitor (Januvia **OR** Onglyza)
  7. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Creatinine clearance
     - Assessment of volume status and correction of existing hypovolemia
     - Risk factor assessment for development of ketoacidosis
  8. The estimated glomerular filtration rate is > 45 mL/min/1.73m^2
  9. There are **NONE** of the following contraindications:
     - Contraindications include:
       - Severe renal impairment (estimated glomerular filtration rate of < 30 mL/min/1.73m^2)
       - Use in end-stage renal disease
       - Individual on dialysis
       - Previous hypersensitivity reaction to any linagliptin containing product
       - Previous hypersensitivity reaction to any empagliflozin containing product

  Initial approval duration: 30 tablets per month for 12 months

- **Criteria for continuation of coverage (renewal request):** Glyxambi (empagliflozin and linagliptin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. The individual has achieved and maintains at least 20% improvement in HgA1c from the baseline
  2. The condition has not progressed or worsened while on therapy
     - Worsening is defined as:
       - Hemoglobin A1c increased while on therapy

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3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Pancreatitis
        - Heart failure
        - Ketoacidosis
        - Acute renal injury
        - Bullous pemphigoid
        - Urinary tract or genital tract infections
        - Necrotizing fasciitis of the perineum (Fournier's Gangrene)

5. There are no significant interacting drugs

Renewal duration: 30 tablets per month for 12 months

Description:

Glyxambi® (empagliflozin and linagliptin) is a 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. It is a combination of a sodium-glucose co-transporter 2 (SGLT2) inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor. It is not recommended for individuals with type 1 diabetes or for the treatment of diabetic ketoacidosis.

SGLT2 is a family of membrane proteins that are responsible for the transport of glucose across the brush border membrane of the proximal renal tubule and across the intestinal lumen. This co-transporter moves sodium and glucose into cells using the sodium gradient produced by sodium-potassium ATPase pumps. There are 2 subtypes of transporters; SGLT1 and SGLT2. SGLT1 is found in the brain, skeletal muscle, lungs, liver, and mucosa of the small intestines, heart, and the latter segment of the proximal tubules of the kidney. SGLT2 is expressed in the early proximal renal tubules and is responsible for the majority (approximately 90%) of the reabsorption of filtered glucose from the tubular lumen. By this mechanism, glucose is reabsorbed into the circulation.

Inhibitors of SGLT2 reduce reabsorption of filtered glucose and lower the renal threshold for glucose (RTG) in a dose dependent manner, resulting in an increase in urinary glucose excretion; overall serum glucose decreases. Examples of SGLT2 inhibitors that are available as single entity formulations include: Invokana™ (canagliflozin), Farxiga® (dapagliflozin), and Jardiance® (empagliflozin). There are several combination products that contain a SGLT2 inhibitor with another agent for the treatment of type 2 diabetes mellitus. Other SGLT2 compounds under investigation include: ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, and tofogliflozin.

Clinical studies on the use of various inhibitors of SGLT2 reveal the following: improvement in hemoglobin A1C (HgbA1C), reduction in fasting plasma glucose, improved postprandial glucose, lower systolic blood pressure, and

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weight loss. Clinical studies also reveal a dose related increase in low-density lipoprotein-C (LDL-C), hyperkalemia, hypermagnesemia, hyperphosphatemia, hypovolemia, and a higher incidence of genital mycotic infections in both men and women. Jardiance® (empagliflozin) is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established, stable, atherosclerotic cardiovascular disease. However, the effectiveness of Glyxambi® on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has not been established.

The DPP-4 enzyme degrades incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are released by the intestine at a low basal level throughout the day, and levels increase in response to a meal. These hormones serve to increase the glucose-dependent synthesis of insulin, increase insulin secretion from pancreatic beta cells, suppress glucagon secretion in a glucose-dependent manner, and slow gastric emptying. GLP-1 and GIP are rapidly inactivated by DPP-4. Inhibition of DPP-4 results in an increase in serum concentration of GLP-1 and GIP, resulting in reduced fasting and postprandial blood glucose concentrations in patients with type 2 diabetes mellitus.

Examples of DPP-4 inhibitors include: Nesina™ (alogliptin), Tradjenta® (linagliptin), Onglyza® (saxagliptin), and Januvia® (sitagliptin).

Several recent guidelines on treatment of type 2 diabetes mellitus have been published. Each guideline analyzes the current literature and makes recommendations on treatment based on the strength of the clinical evidence and incorporates expert opinion. Each guideline suggests that a patient centered approach be implemented in the treatment of type 2 diabetes mellitus that takes into account multiple factors such as medication effectiveness and safety, patient preferences, patient co-morbidities, and cost of medication to name a few.

The guidelines suggest metformin as the generally accepted first line single agent for treatment. When monotherapy does not achieve or maintain target hemoglobin A1c (HbgA1c), the guidelines recommend adding another agent. However, due to limited comparative studies and limited long-term information, uniform agreement on the best agent to combine with metformin was not stated by the guidelines. Potential second line therapy includes selection of an agent from one of the following categories; a sulfonylurea, a meglitinide, a thiazolidindione, a dipeptidyl peptidase-4 inhibitor, a glucagon-like peptide-1 agonist, or an alpha glucosidase inhibitor. The guidelines state selection of one of these agents should take into account other patient variables to implement a patient centered approach to therapy. Insulin may be added at any point, especially when serum glucose levels are substantially elevated and/or the individual has significant hyperglycemic symptoms.

Resources:

Glyxambi product information accessed 04-24-18, 04-22-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ddbab689-f76c-488c-9613-4168d41dd730

Glyxambi®. Package Insert. Revised by manufacturer 3/2017. Accessed 05-01-2017.

Glyxambi®. Package Insert. Reference ID 3694657. Revised by manufacturer 1/2015. Accessed 03-23-2015.

2009 National Institute for Health and Clinical Excellence: Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. Available from www.nice.org.uk/CG87ShortGuideline

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2010 National Institute for Health and Care Excellence: The management of Type 2 diabetes. NICE clinical guideline 87

2012 Diabetes Care: Management of hyperglycemia in Type 2 diabetes: A patient-centered approach. Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee: Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013; 37 (Suppl 1): S1-S212

American Diabetes Association. Approaches to Glycemic Treatment. Section 7 in Standards of Medical Care in Diabetes. Diabetes Care 2015; 38 (Suppl. 1):S41-S48.

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.