STEP THERAPY POLICY

POLICY: Diabetes – Sodium Glucose Co-Transporter-2 Inhibitors Step Therapy Policy

- Brenzavvy™ (bexagliflozin tablets – TheracosBio)
- Farxiga® (dapagliflozin tablets – Bristol-Myers Squibb)
- Invokana® (canagliflozin tablets – Janssen)
- Invokamet® (canagliflozin and metformin hydrochloride tablets – Janssen)
- Invokamet® XR (canagliflozin and metformin hydrochloride extended-release tablets – Janssen)
- Jardiance® (empagliflozin tablets – Boehringer Ingelheim/Lilly)
- Segluromet® (ertugliflozin and metformin tablets – Merck)
- Steglatro® (ertugliflozin tablets – Merck)
- Synjardy® (empagliflozin/metformin hydrochloride tablets – Boehringer Ingleheim/ Lilly)
- Synjardy® XR (empagliflozin/metformin extended-release tablets – Boehringer Ingleheim/Lilly)
- Xigduo® XR (dapagliflozin/metformin extended-release tablets – Bristol-Meyers Squibb)

REVIEW DATE: 05/03/2023; selected revision 09/27/2023

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Brenzavvy, Farxiga, Invokana, Jardiance, and Steglatro are sodium glucose co-transporter-2 (SGLT-2) inhibitors indicated as an adjunct to diet and exercise to improve glycemic control in adults with **type 2 diabetes**.[1-4] Jardiance is also

indicated in pediatric patients ≥ 10 years of age with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control.[3]

The SGLT-2 inhibitors also possess the following additional indications in patients with diabetes:

- Jardiance: To reduce the risk of cardiovascular (CV) death in adults with type 2 diabetes mellitus and established CV disease.
- Invokana: 1) To reduce the risk of major adverse CV events in adults with type 2 diabetes mellitus and established CV disease; AND 2) To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria.
- Farxiga: To reduce the risk of hospitalization for heart failure (HHF) in adults with type 2 diabetes mellitus and established CV disease or multiple CV risk factors.

In addition to indications in diabetes, Farxiga and Jardiance are indicated for the following indications in patients with and without diabetes:[1,3]

- **Heart failure,** to reduce the risk of CV death, HHF, and urgent heart failure visits in adults with heart failure (included both reduced and preserved ejection fraction).
- **Chronic kidney disease,** to reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Guidelines

Diabetes

The American Diabetes Association Standards of Care (2023) note that first-line therapy for type 2 diabetes depends on comorbidities, patient-centered treatment factors, and management needs; it generally includes metformin and comprehensive lifestyle modification.[5] Other medications (glucagon-like peptide-1 receptor agonists, SGLT-2 inhibitors), with or without metformin based on glycemic needs, are appropriate initial therapy for individuals with type 2 diabetes with or at high risk of atherosclerotic CV disease, heart failure, and/or chronic kidney disease. It is noted that an agent with proven benefit should be utilized; with "proven benefit" referring to a label indication.

Heart Failure

The American College of Cardiology (ACC) Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment was updated in 2022.[6] In patients with symptomatic chronic heart failure with reduced ejection fraction, SGLT-2 inhibitors (Farxiga or Jardiance) are recommended to reduce hospitalization for heart failure and CV mortality, irrespective of the presence of type 2 diabetes (class 1 recommendation, level of evidence A). In patients with heart failure with preserved ejection fraction, SGLT-2 inhibitors (Jardiance) can be beneficial in decreasing heart failure hospitalizations and CV mortality, irrespective of the presence of type 2 diabetes (class 2a recommendation, level of evidence B-R).

The ACC Expert Consensus Decision Pathway on Management of Heart Failure with Preserved Ejection Fraction (2023) recommends that all individuals with heart failure with preserved ejection fraction be started on an SGLT-2 inhibitor unless contraindicated.[10] SGLT-2 inhibitors are noted to have demonstrated significant CV benefits in individuals without type 2 diabetes, particularly in individuals with HF. In such patients, SGLT-2 inhibitors have significantly reduced the risk of hospitalization for HF and CV death across all ejection fraction subgroups. Clinical trials with Jardiance and Farxiga are mentioned. For both agents, a significant decrease in HHF was observed.

Kidney Disease

In patients with diabetes and CKD, the Kidney Diseases – Improving Global Outcomes (KDIGO) guidelines for diabetes management in CKD (2022) recommend first-line pharmacotherapy with metformin and an SGLT-2 inhibitor with documented kidney or CV benefit (Invokana, Farxiga, and Jardiance).[7]

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product, and the use of a Step 2 Product prior to the use of a Step 3 Product. If the Step Therapy rule is not met for a Step 2 or Step 3 Product at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Diabetes – Sodium Glucose Co-Transporter-2 Inhibitors product(s) is(are) covered as medically necessary when the following step therapy criteria is(are) met. Any other exception is considered not medically necessary.

- **Requests for a Step 2 Product:** A patient with a history of one of the following within the 130-day look-back period is excluded from Step Therapy:
  - One Step 1 Product; OR
  - One of the following metformin-containing products: Fortamet ER, Glumetza ER, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), glyburide/metformin, glipizide/metformin, Actoplus Met, pioglitazone/metformin, Kazano, alogliptin/metformin, Jentadueto, Jentadueto XR, Kombiglyze XR, saxagliptin/metformin extended-release, Janumet, Janumet XR; OR
  - One Step 2 Product; OR
  - One Step 3 Product.
- **Requests for a Step 3 Product:** A patient with a history of one Step 2 Product within the 130-day look-back period is excluded from Step Therapy.

Step 1: generic metformin, generic metformin-extended release (generic to Glucophage XR only)

Step 2: Farxiga, Jardiance, Segluromet, Steglatro, Synjardy, Synjardy XR, Xigduo XR

Step 3: Brenzavvy, Invokana, Invokamet, Invokamet XR

CRITERIA

Step 2 Products

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.
Note: A trial of one of the following metformin-containing products also satisfies the requirement: Fortamet ER, Glucophage (obsolete), Glucophage XR (obsolete), Glumetza ER, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet ER and Glumetza ER), glyburide/metformin, glipizide/metformin, Actoplus Met, pioglitazone/metformin, Actoplus Met XR (obsolete), repaglinide/metformin (obsolete), Kazano, alogliptin/metformin, Jentadueto, Jentadueto XR, Kombiglyze XR, saxagliptin/metformin extended-release, Janumet, Janumet XR.

2. If the patient has tried one Step 2 Product, approve the requested Step 2 Product.

3. If the patient has tried one Step 3 Product, approve the requested Step 2 Product.

4. If the patient will be initiating dual therapy with metformin AND Farxiga, Jardiance, or Steglatro, approve Farxiga, Jardiance, or Steglatro.

5. If the patient has a contraindication to metformin, according to the prescriber, approve Farxiga, Jardiance, or Steglatro.
Note: Examples of contraindications to metformin include acute or chronic metabolic acidosis, including diabetic ketoacidosis.

6. If the patient has heart failure with reduced ejection fraction, approve Farxiga or Jardiance.

7. If the patient has heart failure with preserved ejection fraction, approve Farxiga or Jardiance.

8. If the patient has chronic kidney disease, approve Farxiga or Jardiance.

9. If the patient has atherosclerotic cardiovascular disease or, according to the prescriber, the patient has at least two risk factors for cardiovascular disease, approve Farxiga or Jardiance.

Step 3 Products

1. If the patient has tried one Step 2 Product, approve a Step 3 Product.

Note: A trial of a Step 1 Product is required prior to a Step 2 Product, unless exception criteria are met.

REFERENCES

1. Farxiga® tablets [prescribing information]. Wilmington, DE: AstraZeneca; May 2023.
2. Invokana® tablets [prescribing information]. Titusville, NJ: Janssen; October 2022.
3. Jardiance® tablets [prescribing information]. Ridgefield, CT and Indianapolis, IN: Boehringer Ingelheim/Lilly; September 2023.
4. Steglatro® tablets [prescribing information]. Whitehouse Station, NJ: Merck; October 2022.
5. American Diabetes Association. Standards of medical care in diabetes – 2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S291.
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(8):e153-e639.
7. Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International.* 2022;102:974-989.
8. The EMPA-KIDNEY Collaborative group. Empagliflozin in patients with Chronic Kidney Disease. *N Engl J Med.* 2023; 388:117-127.
9. Solomon SD, McMurray JJV, Claggett B, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387(12):1089-109.
10. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction. *JACC*. 2023;81(18):1835-1878.
11. Brenzavvy™ tablets [prescribing information]. Marlborough, MA: TheracosBio; January 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Step 1 Products:** The Step 1 Products were revised such that only metformin and metformin extended-release (generic to Glucophage XR only) are listed in Step 1. A Note was added that the following metformin-containing products also satisfy the requirement for a Step 1 trial (previously, these products were also listed in Step 1): Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet, metformin oral solution, Riomet ER, metformin extended-release (generics to Fortamet and Glumetza), glyburide/metformin, glipizide/metformin, Actoplus Met, pioglitazone/metformin, Actoplus Met XR, repaglinide/metformin, Kazano, alogliptin/metformin, Jentadueto, Jentadueto XR, Kombiglyze XR, Janumet, Janumet XR. Of note, Glucovance was removed from this list (obsolete).	05/11/2022
Selected Revision	**Criteria:** An exception was added that if the patient has atherosclerotic cardiovascular disease or, according to the prescriber, the patient has at least two risk factors for cardiovascular disease, approve Farxiga or Jardiance.	08/31/2022
Annual Revision	**Automation:** The following products were removed from the automation (obsolete): Glucophage, Glucophage XR, repaglinide/metformin, Actoplus Met XR. Glumetza and Fortamet were clarified to be Glumetza ER and Fortamet ER. **Criteria Step 2 Products:** For patients requesting a Step 2 product, the note was updated to reflect that Glucophage, Glucophage XR, repaglinide/metformin, and Actoplus Met XR are obsolete (these still count towards a trial of a Step 1 product). Additionally, Glumetza and Fortamet were clarified to be Glumetza ER and Fortamet ER.	05/03/2023

	For patients requesting a Step 2 product with heart failure with preserved ejection fraction, Farxiga was added to the agent approved. Previously only Jardiance was approved. For patients requesting a Step 2 product with chronic kidney disease, Jardiance was added to the agent approved. Previously, only Farxiga was approved.	
DEU Revision	Updated indication in the overview for Farxiga to include expanded heart failure indication.	05/09/2023
Selected Revision	**Automation:** Saxagliptin/metformin extended-release (generic to Kombiglyze XR) was added to the list of metformin-containing products. **Step 3 Products:** Benzavvy was added to Step 3.	09/27/2023