STEP THERAPY POLICY

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

- Brenzavvy™ (bexagliflozin tablets – TheracosBio)
- Farxiga® (dapagliflozin tablets – Bristol-Myers Squibb, authorized
- generic)
- 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, authorized generic)

REVIEW DATE: 05/01/2024; selected revision 08/07/2024, 09/18/2024 (effective 01/01/2025), and 11/20/2024

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Brenzavvy, dapagliflozin, 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] Dapagliflozin and Jardiance are also indicated in pediatric patients ≥ 10 years of age with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control.[1,3]

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.
- Dapagliflozin: 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, dapagliflozin 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 (2024) 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. American Association of Clinical Endocrinology (AACE) Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm (2023) makes similar recommendations.[12] 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 (dapagliflozin or Jardiance) are recommended to reduce HHF 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). Note: This does not reflect the updated indication for dapagliflozin in patients with preserved ejection fraction.

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 heart failure. In such patients, SGLT-2 inhibitors have significantly reduced the risk of HHF and CV death across all ejection fraction subgroups. Clinical trials with Jardiance and dapagliflozin are mentioned. For both agents, a significant decrease in HHF was observed.

Kidney Disease

Kidney Diseases Improving Global Outcomes (KDIGO) 2024 guidelines for the clinical evaluation and management of chronic kidney disease recommend treating patients with type 2 diabetes, chronic kidney disease, and an eGFR ≥ 20 mL/min/1.73 m^2 with an SGLT-2 inhibitor.[13] Once an SGLT-2 inhibitor is initiated, it is reasonable to continue the agent, even if the eGFR falls to < 20 mL/min/1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated. In adults with chronic kidney disease, an SGLT-2 inhibitor is recommended for patients with eGFR ≥ 20 mL/min/1.73 m^2 with urine albumin:creatinine ratio ≥ 200 mg/g or with heart failure, irrespective of the level of albuminuria. SGLT-2 inhibitors are also recommended in adults with eGFR ≥ 20 to ≤ 45 mL/min/1.73 m^2 with urine albumin:creatinine ratio < 200 mg/g.

In patients with diabetes and chronic kidney disease, the KDIGO guidelines for diabetes management in chronic kidney disease (2022) recommend first-line pharmacotherapy with metformin and an SGLT-2 inhibitor with documented kidney or CV benefit (Invokana, dapagliflozin, 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.

- **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: 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, sitagliptin/metformin (authorized generic to Zituvimet), Zituvimet, Zituvimet 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, Synjardy, Synjardy XR, Xigduo XR

Step 3: Brenzavvy, Invokana, Invokamet, Invokamet XR, dapagliflozin (authorized generic to Farxiga), dapagliflozin/metformin extended-release (authorized generic to Xigduo XR), Segluromet, Steglatro

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.

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 (obsolete), 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, sitagliptin/metformin (authorized generic to Zituvimet), Zituvimet, Zituvimet 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 or Jardiance, approve Farxiga or Jardiance.

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

6. If the patient has heart failure, approve Farxiga or Jardiance.

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

8. 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; September 2023.
2. Invokana® tablets [prescribing information]. Titusville, NJ: Janssen; July 2023.
3. Jardiance® tablets [prescribing information]. Ridgefield, CT and Indianapolis, IN: Boehringer Ingelheim/Lilly; September 2023.
4. Steglatro® tablets [prescribing information]. Whitehouse Station, NJ: Merck; September 2023.
5. American Diabetes Association. Standards of medical care in diabetes – 2024. *Diabetes Care*. 2024;47(Suppl 1):S1-S321.
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; September 2023.
12. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. *Endocr Pract.* 2023;29:305-340.

13. Kidney Diseases Improving Global Outcomes (KDIGO). KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* 2024;105(4S):S117-S314.

HISTORY

Type of Revision	Summary of Changes	Review Date
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 a patient 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. For a patient 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.	05/03/2023
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:** Brenzavvy was added to Step 3.	09/27/2023
Selected Revision	**Step 3 Products:** dapagliflozin (authorized generic to Farxiga) and dapagliflozin/metformin extended-release (authorized generic to Xigduo XR) were added to Step 3.	02/21/2024
Annual Revision	**Automation:** Fortamet ER was removed from the list of metformin-containing products (obsolete). **Criteria Step 2 Products:** For a patient requesting a Step 2 product, the note was updated to reflect that Fortamet ER is obsolete (this still counts towards a trial of a Step 1 product). Criteria for a patient with heart failure with reduced ejection fraction and a patient with heart failure with preserved ejection fraction were combined into one criterion (previously, each criterion approved Farxiga or Jardiance). For the new combined criterion, Farxiga or Jardiance is approved for a patient with heart failure.	05/01/2024
DEU Revision	Updated indication in the overview for dapagliflozin to include expanded indication in pediatric patients.	06/13/2024
Selected Revision	**Automation:** Sitagliptin/metformin (authorized generic) was added to automation for one metformin-containing product. **Criteria:** For a patient requesting a Step 2 product, the note was updated to add sitagliptin/metformin (authorized generic) to the list of metformin-containing products.	08/07/2024
Selected revision	The following changes are effective 01/01/2025: **Step 2 Products:** Steglatro and Segluromet were removed (moved to Step 3).	09/18/2024 (effective 01/01/2025)

	Step 3 Products: Steglatro and Segluromet were added (previously, Step 2). **Criteria for Step 2 Products:** Steglatro was removed from the following criterion: In a patient initiating dual therapy with metformin AND Farxiga, Jardiance, or Steglatro, approve Farxiga, Jardiance, or Steglatro. The criterion continues to approve Farxiga or Jardiance in a patient initiating dual therapy with metformin and Farxiga or Jardiance. Steglatro was removed from the following criterion: In a patient with a contraindication to metformin, according to the prescriber, approve Farxiga, or Jardiance, or Steglatro. The criterion continues to approve Farxiga or Jardiance in a patient with a contraindication to metformin, according to the prescriber.	
Selected Revision	**Automation:** Zituvimet and Zituvimet XR were added to automation for one metformin-containing product. **Criteria:** For a patient requesting a Step 2 product, the note was updated to add Zituvimet and Zituvimet XR to the list of metformin-containing products.	11/20/2024