

## Clinical Policy: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

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Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

### Description

The following agents contain a sodium-glucose co-transporter 2 (SGLT2) inhibitor and require prior authorization: canagliflozin (Invokana®), canagliflozin/metformin (Invokamet®, Invokamet® XR), dapagliflozin (Farxiga®), dapagliflozin/metformin (Xigduo® XR), dapagliflozin/saxagliptin (Qtern®), dapagliflozin/saxagliptin/metformin (Qternmet® XR), empagliflozin (Jardiance®), empagliflozin/linagliptin (Glyxambi®), empagliflozin/linagliptin/metformin (Trijardy™ XR), empagliflozin/metformin (Synjardy®, Synjardy® XR), ertugliflozin (Steglatro™), ertugliflozin/metformin (Segluromet™), and ertugliflozin/sitagliptin (Steglujan™).

### FDA Approved Indication(s)

SGLT2 inhibitors are indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dapagliflozin-, canagliflozin-, and empagliflozin-containing products are also indicated in adult patients with type 2 diabetes mellitus and established cardiovascular disease (CV) (or multiple cardiovascular risk factors [*dapagliflozin only*]) to:

- Reduce the risk of hospitalization for heart failure (HF) (dapagliflozin)
- Reduce the risk of major adverse CV events: CV death, nonfatal myocardial infarction, and nonfatal stroke (canagliflozin)
- Reduce the risk of CV death (empagliflozin)

Canagliflozin-containing products are additionally indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day.

Farxiga is additionally indicated to reduce the risk of CV death and hospitalization for HF in adults with heart failure with reduced ejection fraction (HFrEF) (New York Heart Association [NYHA] class II-IV).

Limitation(s) of use:

- SGLT2 inhibitors should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. SGLT2 inhibitors may increase the risk of diabetic ketoacidosis.
- Qternmet XR initiation is intended only for patients currently taking metformin.

### Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that SGLT2 inhibitors are **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Type 2 Diabetes Mellitus (must meet all):

1. Diagnosis of type 2 diabetes mellitus;

2. Age  $\geq$  18 years;
3. Member meets one of the following (a or b):
  - a. Failure of  $\geq$  3 consecutive months of metformin, unless contraindicated or clinically significant adverse effects are experienced;
  - b. For medication-naïve members, requested agent is approvable if intended for concurrent use with metformin due to HbA1c  $\geq$  8.5% (drawn within the past 3 months);
4. If request is for a non-preferred SGLT2 inhibitor, member meets one of the following (a, b, c, or d):
  - a. For empagliflozin-containing products: Member has established CV disease (e.g., ASCVD or HF) or diabetic nephropathy;
  - b. For canagliflozin- or dapagliflozin-containing products: Member has established CV disease (e.g., ASCVD or HF), diabetic nephropathy, or multiple risk factors for cardiovascular disease (*see Appendix D*);
  - c. For Glyxambi, Qtern, Qternmet XR, Steglujan, and Trijardy XR: Failure of  $\geq$  3 consecutive months of a preferred SGLT2 inhibitor OR a preferred dipeptidyl peptidase-4 (DPP-4) inhibitor, unless all are contraindicated or clinically significant adverse effects are experienced;
  - d. For all other non-preferred SGLT2 inhibitors: Failure of  $\geq$  3 consecutive months of a preferred SGLT2 inhibitor, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

**Approval duration: 12 months**

**B. Heart Failure** (must meet all):

1. Diagnosis of HFrEF of NYHA Class II, III, or IV;
2. Request is for Farxiga;
3. Prescribed by or in consultation with a cardiologist;
4. Age  $\geq$  18 years;
5. Left ventricular ejection fraction (LVEF) is  $\leq$  40%;
6. Member does not have a diagnosis of type 1 diabetes mellitus;
7. Member is currently receiving standard HF drug therapy at target doses for  $\geq$  4 weeks, including both of the following (a and b) unless clinically significant adverse effects are experienced or all are contraindicated:
  - a. Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or Entresto®;
  - b. Beta blocker;
8. Dose does not exceed 10 mg (1 tablet) per day.

**Approval duration: 12 months**

**C. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Type 2 Diabetes Mellitus** (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

**Approval duration: 12 months**

**B. Heart Failure** (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Farxiga for HFrEF and has received this medication for at least 30 days;

2. Request is for Farxiga;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 10 mg (1 tablet) per day.

**Approval duration: 12 months**

**C. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

**Approval duration: Duration of request or 12 months (whichever is less);** or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

AACE: American Association of Clinical Endocrinologists  
 ACE: American College of Endocrinology  
 ADA: American Diabetes Association  
 ASCVD: atherosclerotic cardiovascular disease  
 CV: cardiovascular  
 DPP-4: dipeptidyl peptidase-4  
 ER: extended-release

FDA: Food and Drug Administration  
 GLP-1: glucagon-like peptide-1  
 HbA1c: glycated hemoglobin  
 HFrEF: heart failure with reduced ejection fraction  
 IR: immediate-release  
 LVEF: left ventricular ejection fraction  
 SGLT2: sodium-glucose co-transporter 2

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

| Drug Name  | Dosing Regimen   | Dose Limit/ Maximum Dose  |
|--|--|---|
| metformin (Fortamet <sup>®</sup> , Glucophage <sup>®</sup> , Glucophage <sup>®</sup> XR, Glumetza <sup>®</sup> ) | Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks<br><br>Extended-release:<br><ul style="list-style-type: none"> <li>• Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week</li> <li>• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week</li> </ul> | Regular-release: 2,550 mg/day<br><br>Extended-release: 2,000 mg/day |
| Segluromet (ertugliflozin/metformin)   | Individualized dose PO BID   | 15/2,000 mg/day   |
| Steglatro (ertugliflozin)  | 5 mg PO QD   | 15 mg/day   |
| <b>ACEIs</b>   |  |   |
| captopril (Capoten <sup>®</sup> )  | Initially, 6.25 mg PO 3 times daily, then increase to 50 mg PO 3 times daily if tolerated.   | 450 mg/day  |
| enalapril (Vasotec <sup>®</sup> , Epaned <sup>®</sup> )  | Initially, 2.5 mg PO twice daily, then increase to 10 to 20 mg PO twice daily if tolerated.  | 40 mg/day   |

| Drug Name   | Dosing Regimen  | Dose Limit/<br>Maximum Dose  |
|---|---|--|
| fosinopril (Monopril <sup>®</sup> )   | Initially, 5 to 10 mg PO once daily, then increase to 40 mg/day if tolerated.   | 80 mg/day  |
| lisinopril (Prinivil <sup>®</sup> , Zestril <sup>®</sup> , Qbrelis <sup>®</sup> ) | Initially, 2.5 to 5 mg PO once daily, then increase to 20 to 40 mg/day if tolerated.  | 80 mg/day  |
| perindopril (Aceon <sup>®</sup> )   | Initially, 4 mg PO once daily for 2 weeks, then increase to 8 mg PO once daily if tolerated.  | 16 mg/day  |
| quinapril (Accupril <sup>®</sup> )  | Initially, 5 mg PO twice daily, then increase to 20 mg PO twice daily if tolerated.   | 80 mg/day  |
| ramipril (Altace <sup>®</sup> )   | Initially, 2.5 mg PO once daily. Gradually titrate to 5 mg/day PO, then increase if tolerated to the target dosage of 10 mg/day PO, given in 1 to 2 divided doses.  | 20 mg/day  |
| trandolapril (Mavik <sup>®</sup> )  | Initially, 1 mg PO once daily, then increase to 4 mg/day if tolerated.  | 8 mg/day   |
| <b>ARBs</b>   |   |  |
| candesartan (Atacand <sup>®</sup> )   | Initially, 4 to 8 mg PO once daily, then increase to 32 mg/day if tolerated.  | 32 mg/day  |
| losartan (Cozaar <sup>®</sup> )   | Initially, 25 to 50 mg PO once daily, then increase to 50 to 150 mg/day if tolerated.   | 100 mg/day   |
| telmisartan (Micardis <sup>®</sup> )  | 80 mg PO once daily   | 80 mg/day  |
| valsartan (Diovan <sup>®</sup> )  | Initially, 20 to 40 mg PO twice daily, then increase dose to 160 mg PO twice daily if tolerated.  | 320 mg/day   |
| <b>ARNI/ARB</b>   |   |  |
| Entresto <sup>®</sup> (sacubitril/valsartan)                                      | The recommended starting dose is 49/51 mg (sacubitril/valsartan) PO BID. Double the dose after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) BID, as tolerated by the patient.  | 194/206 mg/day   |
| <b>Sinoatrial Node Modulator</b>  |   |  |
| Corlanor <sup>®</sup> (ivabradine)  | Initially 2.5 mg or 5 mg PO BID. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg BID.   | 15 mg/day  |
| <b>Beta-Blockers Recommended for HF</b>   |   |  |
| bisoprolol (Zebeta <sup>®</sup> )   | <b>HF</b><br>Initially, 1.25 mg PO QD for 48 hours, then 2.5 mg QD for the first month, then 5 mg QD.   | 10 mg/day  |
| carvedilol (Coreg <sup>®</sup> , Coreg CR <sup>®</sup> )                          | <b>HF</b><br><u>Immediate-release:</u> Initially, 3.125 mg PO BID for 2 weeks. Dosage may be subsequently increased to 6.25, 12.5, and then 25 mg PO BID over successive intervals of at least 2 weeks.<br><u>Extended-release:</u> Initially, 10 mg PO QD for 2 weeks. Dosage may be subsequently increased to 20, 40, and then 80 mg PO QD over successive intervals of at least 2 weeks. | Immediate-release:<br>100 mg/day<br><br>Extended-release:<br>80 mg/day |
| metoprolol succinate extended release (Toprol XL <sup>®</sup> )                   | <b>HF</b><br>25 mg PO QD for 2 weeks in patients with NYHA class II HF, or 12.5 mg PO QD in patients with more severe HF. Double the dose every 2 weeks as tolerated, up to the target dosage of 200 mg PO QD.  | 200 mg/day   |

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - History of serious hypersensitivity reaction to the requested drug product
  - Moderate to severe renal impairment\*, end-stage renal disease, or dialysis  
*\*Minimum degree of renal impairment varies per agent; refer to individual prescribing information*
  - Metabolic acidosis, including diabetic ketoacidosis (*metformin-containing products only*)
- Boxed warning(s): lactic acidosis (*metformin-containing products only*)

*Appendix D: General Information*

- A double-blind, placebo-controlled dose-response trial by Garber et al. found the maximal efficacy of metformin to occur at doses of 2,000 mg. However, the difference in adjusted mean change in HbA1c between the 1,500 and 2,000 mg doses was 0.3%, suggesting that the improvement in glycemic control provided by the additional 500 mg may be insufficient when HbA1c is > 7%.
- Per the 2020 American Diabetes Association (ADA) and 2020 American Association of Clinical Endocrinologists and American College of Endocrinology (AAACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, glucagon-like peptide 1 [GLP-1] receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target per the ADA (≥ 7.5% per the AAACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AAACE/ACE).
    - Starting with combination therapy with insulin may be considered for patients with baseline HbA1c > 10% per the ADA (> 9% if symptoms are present per the AAACE/ACE).
  - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination therapy with insulin should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.
- Although Invokana is currently the only SGLT2 inhibitor with a labeled indication for diabetic nephropathy, Farxiga and Jardiance have also demonstrated renal protective effects. The 2020 ADA guidelines recommend SGLT2 inhibitors be considered when treating type 2 diabetic patients with renal concerns, noting that Farxiga, Jardiance, and Invokana all confer renal benefit, with no preference for one over the other
  - Farxiga DECLARE-TIMI 58: The cardiorenal secondary composite outcome (sustained decline of at least 40% in eGFR to less than 60 mL/min/1.73 m<sup>2</sup>, end stage renal disease (ESRD), or death from renal or CV causes) was significantly reduced with Farxiga compared to placebo (HR 0.76, 95% CI 0.67-0.87; p < 0.0001); excluding death from CV causes, the HR for the renal-specific outcome was 0.53 (95% CI 0.43-0.66; p < 0.0001). There was a 46% reduction in sustained decline in eGFR by at least 40% to less than 60 mL/min/1.73 m<sup>2</sup> (120 [1.4%] vs 221 [2.6%]; HR 0.54 [95% CI 0.43-0.67]; p < 0.0001). The risk of ESRD or renal death was also lower in the Farxiga group than in the placebo group (11 [0.1%] vs 27 [0.3%]; HR 0.41 [95% CI 0.20-0.82]; p = 0.012).
  - Jardiance EMPA-REG Outcome: Analysis of secondary outcomes yielded a reduction of risk for incident of or worsening nephropathy (HR 0.61 [95% CI 0.53-0.70]), progression to urine albumin to creatinine ratio (UACR) > 300 mg/g (HR 0.62 [95% CI 0.54-0.72]), composite consisting doubling of serum creatinine, initiation of renal replacement therapy, and death from ESRD (HR 0.54 [95% CI 0.40-0.75]).
- Examples of CV risk factors may include but are not limited to: dyslipidemia, hypertension, obesity/overweight, a family history of premature coronary disease, and smoking.

- According to the ADA, ASCVD includes coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin.
- Although Farxiga and Invokana are the only SGLT2 inhibitors with labeled indications for reducing the risk of HHF, Jardiance has also been shown to reduce the risk of HHF. The 2020 ADA guidelines acknowledge Farxiga along with Jardiance and Invokana as agents which reduce the risk of HHF, without a preference for one agent over the other. Any of the three can be used in T2DM patients with established HF; however, the guidelines recommend only Jardiance or Invokana for patients with established ASCVD.
  - Jardiance EMPA-REG Outcome, patients with established ASCVD: The primary outcome (composite of death from CV causes, nonfatal MI, or non-fatal stroke) was reduced with Jardiance compared to placebo (HR 0.86, 95% CI 0.74 – 0.99; p = 0.04). Analysis of secondary outcomes yielded a reduction in hospitalization for heart failure when treated with Jardiance compared to placebo (HR 0.65, 95% CI 0.50 – 0.85; p = 0.002).
  - Invokana CANVAS Program, patients with established ASCVD or multiple ASCVD risk factors: The primary outcome (composite of death from CV causes, nonfatal MI or nonfatal stroke) was reduced with Invokana compared to placebo (HR 0.86, 95% CI 0.75 – 0.97; p = 0.02). Analysis of secondary outcomes yielded a reduction in hospitalization for heart failure when treated with Invokana compared to placebo (HR 0.67, 95% CI 0.52 – 0.87).
- In August 2020, the FDA removed the boxed warning regarding the risk of leg and foot amputations from the canagliflozin prescribing information. Although the risk is still present (and continues to be described in the Warnings and Precautions section of the prescribing information), the FDA notes the significantly enhanced benefit of canagliflozin (e.g., effects in heart and kidney disease) relative to said risk, which safety information from recent trials suggest is lower than previously described.

**V. Dosage and Administration**

| Drug Name   | Dosing regimen   | Maximum Dose      |
|---|--|-------------------|
| Farxiga (dapagliflozin)                           | 5 mg PO QD<br><br>To reduce the risk of hospitalization for HF in T2DM patients and the risk of CV death and hospitalization in adults with HFrEF, the recommended dose is 10 mg PO QD | 10 mg/day         |
| Glyxambi (empagliflozin/linagliptin)              | 10/5 mg PO QD  | 25/5 mg/day       |
| Invokamet (canagliflozin/metformin)               | One 50/500 mg tablet PO BID  | 300/2,000 mg/day  |
| Invokamet XR (canagliflozin/metformin)            | Two 50/500 mg tablets PO QD  | 300/2,000 mg/day  |
| Invokana (canagliflozin)                          | 100 mg PO QD   | 300 mg/day        |
| Jardiance (empagliflozin)                         | 10 mg PO QD  | 25 mg/day         |
| Qtern (dapagliflozin/saxagliptin)                 | One 5/5 mg tablet PO QD  | 10/5 mg/day       |
| Qternmet XR (dapagliflozin/saxagliptin/metformin) | Individualized dose PO QD  | 10/5/2,000 mg/day |
| Segluromet (ertugliflozin/metformin)              | Individualized dose PO BID   | 15/2,000 mg/day   |
| Steglatro (ertugliflozin)                         | 5 mg PO QD   | 15 mg/day         |
| Steglujan (ertugliflozin/sitagliptin)             | One 5/100 mg tablet PO QD  | 15/100 mg/day     |
| Synjardy (empagliflozin/metformin)                | Individualized dose PO BID   | 25/2,000 mg/day   |
| Synjardy XR (empagliflozin/metformin)             | Individualized dose PO QD  | 25/2,000 mg/day   |
| Trijardy XR (empagliflozin/linagliptin/metformin) | Individualized dose PO QD  | 25/5/2,000 mg/day |
| Xigduo XR (dapagliflozin/metformin)               | Individualized dose PO QD  | 10/2,000 mg/day   |

**VI. Product Availability**

| Drug Name  | Availability   |
|--|--|
| Farxiga (dapagliflozin)                            | Tablets: 5 mg, 10 mg   |
| Glyxambi (empagliflozin/linagliptin)               | Tablets: 10/5 mg, 25/5 mg  |
| Invokamet (canagliflozin/metformin)                | Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg                |
| Invokamet XR (canagliflozin/metformin)             | Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg                |
| Invokana (canagliflozin)                           | Tablets: 100 mg, 300 mg  |
| Jardiance (empagliflozin)                          | Tablets: 10 mg, 25 mg  |
| Qtern (dapagliflozin/saxagliptin)                  | Tablet: 5/5 mg, 10/5 mg  |
| Qternmet XR (dapagliflozin/saxagliptin/metformin)  | Tablets: 2.5/2.5/1,000 mg, 5/2.5/1,000 mg, 5/5/1000 mg, 10/5/1,000 mg    |
| Segluromet (ertugliflozin/metformin)               | Tablets: 2.5/500 mg, 2.5/1,000mg, 7.5/500 mg, 7.5/1,000mg                |
| Steglatro (ertugliflozin)                          | Tablets: 5 mg, 15 mg   |
| Steglujan (ertugliflozin/sitagliptin)              | Tablets: 5/100 mg, 15/100 mg   |
| Synjardy (empagliflozin/metformin)                 | Tablets: 5/500 mg, 5/1,000 mg, 12.5/500 mg, 12.5/1,000 mg                |
| Synjardy XR (empagliflozin/metformin)              | Tablets: 5/1,000 mg, 10/1,000 mg, 12.5/1,000 mg, 25/1,000 mg             |
| Trijardy XR (empagliflozin/linagliptin/ metformin) | Tablets: 5/2.5/1,000 mg, 10/5/1,000 mg, 12.5/2.5/1,000 mg, 25/5/1,000 mg |
| Xigduo XR (dapagliflozin/metformin)                | Tablets: 2.5/1,000 mg, 5/500 mg, 5/1,000 mg, 10/500 mg, 10/1,000 mg      |

**VII. References**

- American Diabetes Association. Standards of medical care in diabetes—2020. Diabetes Care. 2020;43 (suppl 1): S1-S212. Updated June 5, 2020. Accessed October 26, 2020.
- Farxiga Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020. Available at: [www.farxiga.com](http://www.farxiga.com). Accessed October 28, 2020.
- Qtern Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2020. Available at: [www.qtern.com](http://www.qtern.com). Accessed October 27, 2020.
- Qternmet XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210874s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210874s000lbl.pdf). Accessed October 27, 2020.
- Xigduo XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2020. Available at: [www.xigduoxr.com](http://www.xigduoxr.com). Accessed October 28, 2020.
- Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020. Available at: [www.invokana.com](http://www.invokana.com). Accessed October 28, 2020.
- Invokamet/Invokamet XR Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020. Available at: [www.invokamet.com](http://www.invokamet.com). Accessed October 28, 2020.
- Jardiance Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; January 2020. Available at: [www.jardiance.com](http://www.jardiance.com). Accessed October 28, 2020.
- Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2020. Available at: [www.glyxambi.com](http://www.glyxambi.com). Accessed October 27, 2020.
- Synjardy Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; January 2020. Available at: [www.synjardy.com](http://www.synjardy.com). Accessed October 28, 2020.
- Synjardy XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; January 2020. Available at: [www.synjardyxr.com](http://www.synjardyxr.com). Accessed October 28, 2020.
- Trijardy XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; January 2020. Available at: [www.trijardy.com](http://www.trijardy.com). Accessed October 27, 2020.
- Steglatro Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; January 2020. Available at [www.steglatro.com](http://www.steglatro.com). Accessed October 28, 2020.
- Segluromet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; January 2020. Available at [www.segluromet.com](http://www.segluromet.com). Accessed October 28, 2020.

15. Steglujan Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; January 2020. Available at [www.steglujan.com](http://www.steglujan.com). Accessed October 27, 2020.
16. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997; 102: 491-497.
17. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. *Endocr Pract.* 2020; 26(1): 107-139.
18. Patorno E, Pawar A, Franklin JM, et al. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. *Circulation* *AHA*; 2019 Jun 18;139(25):2822-2830. doi: 10.1161/CIRCULATIONAHA.118.039177
19. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; 377:644-657. DOI: 10.1056/NEJMoa1611925
20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; 373:2117-2128. DOI:10.1056/NEJMoa150472
21. Yancy C, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol.* 2017 Aug, 70 (6) 776-803.

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| Policy created: adapted from ERX.ST.01 SGLT2 inhibitors; added diagnosis, age, and positive response requirements; criteria added for Invokana’s new FDA indication: diabetic nephropathy; criteria added for Farxiga’s new FDA indication: reduction in risk of hospitalization due to HF in patients with established cardiovascular disease or with multiple cardiovascular risk factors; criteria added for Farxiga/Jardiance for diabetic nephropathy and Invokana/Jardiance for HF as supported by ADA guidelines and published data; criteria added for Invokana for multiple cardiovascular risk factors references as supported by CANVAS Program trials; added Trijardy XR; references reviewed and updated. | 12.03.19 | 02.20             |
| Modified references to parent products (Farxiga, Invokana, and Jardiance) to allow combination products (e.g., dapagliflozin-, canagliflozin-, and empagliflozin-containing products) per previously approved clinical guidance.   | 04.01.20 |                   |
| Criteria added for Farxiga’s new FDA indication: heart failure with reduced ejection fraction.   | 06.02.20 | 08.20             |
| 1Q 2021 annual review: no significant changes; removed lower limb amputation boxed warning for canagliflozin from Appendix C per updated PI; references reviewed and updated.  | 10.28.20 | 02.21             |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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