

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

Reference Number: CP.PMN.14

Effective Date: 03.01.19

Last Review Date: 02.20

Line of Business: 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<sup>®</sup>), canagliflozin/metformin (Invokamet<sup>®</sup>, Invokamet<sup>®</sup> XR), dapagliflozin (Farxiga<sup>®</sup>), dapagliflozin/metformin (Xigduo<sup>®</sup> XR), dapagliflozin/saxagliptin (Qtern<sup>®</sup>), dapagliflozin/saxagliptin/metformin (Qternmet<sup>®</sup> XR), empagliflozin (Jardiance<sup>®</sup>), empagliflozin/linagliptin (Glyxambi<sup>®</sup>), empagliflozin/linagliptin/metformin (Trijardy<sup>™</sup> XR), empagliflozin/metformin (Synjardy<sup>®</sup>, Synjardy<sup>®</sup> XR), and ertugliflozin/sitagliptin (Steglujan<sup>™</sup>).

*\*Please refer to CP.PST.01 Step Therapy for ertugliflozin (Steglatro<sup>™</sup>) and ertugliflozin/metformin (Segluromet<sup>™</sup>).*

**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 (or multiple cardiovascular risk factors [*dapagliflozin only*]) to:

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

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

Limitation(s) of use:

- SGLT2 inhibitors should not be used in patients with type 1 diabetes or for the treatment 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.*

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> 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. HbA1c drawn within the past 3 months is  $\geq$  8.5%, and concurrent use of metformin, unless contraindicated or clinically significant adverse effects are experienced;
4. Request meets one of the following (a, b, or c):
  - a. Failure of  $\geq$  3 consecutive months of Steglatro or Segluromet, unless both are contraindicated or clinically significant adverse effects are experienced;
  - b. Member has established cardiovascular disease (e.g., ASCVD or HF) or diabetic nephropathy, and request is for a formulary empagliflozin-containing product, unless contraindicated or clinically significant adverse effects are experienced;
  - c. Member has multiple risk factors for cardiovascular disease (*see Appendix D*), and request is for a formulary canagliflozin- or dapagliflozin-containing product, 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. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Currently receiving medication via Centene benefit 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. Other diagnoses/indications** (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

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

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

### **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 policies – CP.PMN.53 for Medicaid 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

DPP-4: dipeptidyl peptidase-4

ER: extended-release

FDA: Food and Drug Administration

GLP-1: glucagon-like peptide-1

HbA1c: glycated hemoglobin

HF: heart failure

IR: immediate-release

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 for all relevant lines of business and may require prior authorization.*

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
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  Extended-release: <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  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

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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*), lower limb amputation (*Invokana 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 2019 American Diabetes Association (ADA) and 2019 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/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, dipeptidyl peptidase-4 [DPP-4] inhibitor, SGLT2 inhibitor, glucagon-like peptide 1 [GLP-1] receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c  $\geq 1.5\%$  above their target per the ADA ( $\geq 7.5\%$  per the AACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is  $< 7\%$  ( $\leq 6.5\%$  per the AACE/ACE).
    - Starting with combination injectable therapy (i.e., with GLP-1 receptor agonist or insulin) may be considered for patients with baseline HbA1c  $\geq 10\%$  or  $\geq 2\%$  above their target per the ADA ( $> 9\%$  if symptoms are present per the AACE/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 injectable therapy 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 2019 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 cardiovascular causes) was significantly reduced with Farxiga compared to placebo (HR 0.76, 95% CI 0.67-0.87;  $p < 0.0001$ ); excluding death from cardiovascular 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 cardiovascular risk factors may include but are not limited to: dyslipidemia, hypertension, obesity, 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 2019 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).

## V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Farxiga (dapagliflozin)	5 mg PO QD  To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg PO QD	10 mg/day
Glyxambi (empagliflozin/linagliptin)	One 10/5 mg tablet 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

Drug Name	Dosing Regimen	Maximum Dose
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
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, 5/5/1,000 mg, 10/5/1,000 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

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 Policy created per SDC recommendation based on previously approved clinical guidance: adapted from previously corporate approved policy CP.PST.19; modified to reflect that all SGLT2 inhibitors (except for Steglatro and Segluromet) now require PA (instead of ST), added diagnosis, and added re-direction to Steglatro/Segluromet (with exception for members with ASCVD requesting Jardiance); removed Steglatro and Segluromet from policy (added to CP.PST.01 Step Therapy); added updated indication for ASCVD for Invokana; modified minimum A1c related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines.	10.17.18	02.19
Added Qtern and Qternmet XR with re-direction to the preferred SGLT2 inhibitor Steglatro/Segluromet.	05.08.19	
1Q 2020 annual review: policy updated to include Invokana's new FDA indication: diabetic nephropathy and 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 modified to allow Jardiance for diabetic nephropathy/HF as supported by ADA guidelines/published data (Farxiga and Invokana are not allowed due to formulary status); clarified that established cardiovascular disease can mean ASCVD or HF; added criteria to allow Invokana for patients with multiple cardiovascular risk factors as supported by CANVAS Program trials; added Trijardy XR with re-direction to Steglatro or Segluromet per SDC; references reviewed and updated.	12.03.19	02.20
Modified references to parent products (Farxiga, Invokana, and Jardiance) to allow formulary combination products (e.g., dapagliflozin-, canagliflozin-, and empagliflozin-containing products) per previously approved clinical guidance and SDC clarification.	04.01.20	

### **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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.



The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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