

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

Reference Number: HIM.PA.91

Effective Date: 01.01.15

Last Review Date: 02.20

Line of Business: HIM

[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[®]), dapagliflozin (Farxiga[®]), dapagliflozin/metformin (Xigduo[®] XR), empagliflozin (Jardiance[®]), empagliflozin/linagliptin (Glyxambi[®]), empagliflozin/linagliptin/metformin (Trijardy[™] XR), and empagliflozin/metformin (Synjardy[®]).

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.

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[®] 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 ≥ 18 years;

3. Member meets one of the following (a or b):
 - a. Failure of ≥ 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 ≥ 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 canagliflozin-, dapagliflozin-, and 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): HIM.PHAR.21 for health insurance marketplace.

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): HIM.PHAR.21 for health insurance marketplace.

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 – HIM.PHAR.21 for health insurance marketplace 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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Fortamet [®] , Glucophage [®] , Glucophage [®] XR, Glumetza [®])	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"> Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week 	Regular-release: 2550 mg/day Extended-release: 2,000 mg/day
Steglatro [™] (ertugliflozin)	5 mg PO QD	15 mg/day
Segluromet [™] (ertugliflozin/metformin)	Individualized dose PO BID	15/2,000 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), 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 (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, 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 AAACE/ACE). According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% ($\leq 6.5\%$ per the AAACE/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 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 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 m², 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 m² (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: 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/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 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
Invokana (canagliflozin)	100 mg PO QD	300 mg/day
Jardiance (empagliflozin)	10 mg PO QD	25 mg/day
Synjardy (empagliflozin/metformin)	Individualized dose PO BID	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
Invokana (canagliflozin)	Tablets: 100 mg, 300 mg
Jardiance (empagliflozin)	Tablets: 10 mg, 25 mg
Synjardy (empagliflozin/metformin)	Tablets: 5/500 mg, 5/1,000 mg, 12.5/500 mg, 12.5/1,000 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

1. American Diabetes Association. Standards of medical care in diabetes—2019. *Diabetes Care*. 2019; 42(suppl 1): S1-S193. Updated July 31, 2019. Accessed September 25, 2019.
2. Farxiga Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2019. Available at: www.farxiga.com. Accessed October 24, 2019.
3. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; July 2019. Available at: www.glyxambi.com. Accessed September 26, 2019.
4. Invokamet Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; January 2020. Available at: www.invokamet.com. Accessed February 6, 2020.
5. Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2019. Available at: www.invokana.com. Accessed October 15, 2019.
6. Jardiance Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2018. Available at: www.jardiance.com. Accessed September 26, 2019.
7. Synjardy Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2018. Available at: www.synjardy.com. Accessed September 26, 2019.
8. Xigduo XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2019. Available at: www.xigduoxr.com. Accessed September 26, 2019.
9. 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.
10. Garber AJ, Abrahamson MJ, Barzilay, JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. *Endocr Pract*. 2019; 25(1): 69-100.
11. Steglatro Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; October 2018. Available at www.steglatro.com. Accessed September 26, 2019.
12. Segluromet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; October 2018. Available at www.segluromet.com. Accessed September 26, 2019.

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13. Trijardy XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; January 2020. Available at: www.trijardy.com. Accessed February 5, 2020.
14. 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
15. 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/NEJMoa1504720.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Changed guidelines to new format. Changed wording from requiring trial and failure of 2,000mg of metformin to maximum tolerated dose.	02.16	02.16
Renamed criteria from Invokana to SGLT2 inhibitors to reflect the added variety of products on the formulary and slight reformatting of the template. Clinical changes made to criteria: - Added FDA max dose criteria for each product. - For initial, modified trial of metformin to require doses at least 2,000 mg/day for 3 months (rather than 6 weeks) per ADA guidelines and adjusted approval duration to 6 months to allow for efficacy assessment. - For re-auth, added specific efficacy criteria; removed requirement for adherence.	12.16	02.17
Added age restriction as safety and efficacy have not been established in pediatric populations.	08.18.17	11.17
Removed requirement for diagnosis Removed requirement for A1C submission Changed requirement for Metformin trial to be for 3 months without mandating a specific dose Allow first line use for members with A1C >= 9% References reviewed and updated	11.07.17	02.18
No significant changes: added requirement for the trial of Tradjenta for Glyxambi to align criteria with the requirement in the DPP-4 policy	07.09.18	
Per SDC: modified to reflect that all SGLT2 inhibitors now require PA (instead of ST); added diagnosis; removed re-direction to Tradjenta for Glyxambi; added re-direction to Steglatro/Segluromet for all agents (with exception for members with ASCVD requesting Jardiance).	09.19.18	
1Q 2019 annual review: removed Steglatro since it requires ST rather than PA; added exception for members with ASCVD requesting Invokana per updated FDA indication; modified minimum A1c	10.29.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
related for concurrent use of metformin from 9% to 8.5% based on 2019 ADA guidelines; references reviewed and updated.		
Per SDC, removed Segluomet as PA is no longer required.	10.23.19	
1Q 2020 annual review: 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 as supported by CANVAS Program trials; clarified that established cardiovascular disease can mean ASCVD or HF; added Trijardy XR with re-direction to Steglatro or Segluomet 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

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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.

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