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

Reference Number: HIM.PA.91
Effective Date: 01.01.15
Last Review Date: 02.18
Line of Business: HIM

Revision Log

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

Description

The following are sodium-glucose co-transporter 2 (SGLT2) inhibitors requiring prior authorization: canagliflozin (Invokana®), canagliflozin/metformin (Invokamet®), dapagliflozin (Farxiga®), dapagliflozin/metformin (Xigduo® XR), empagliflozin (Jardiance®), empagliflozin/linagliptin (Glyxambi®), empagliflozin/metformin (Synjardy®), ertugliflozin (Steglatro™), and ertugliflozin/metformin (Segluromet™).

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.

Jardiance is also indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

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 (including 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 ≥ 9%, 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. Request is for Steglatro or Segluromet;
   b. Request is for Jardiance, and member has cardiovascular disease;

c. Failure of ≥ 3 consecutive months of Steglatro or Segluromet, unless both are 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
DPP-4: dipeptidyl peptidase-4
ER: extended-release
FDA: Food and Drug Administration
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
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: • Fortamet, Glumetza: 1000 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: • Fortamet: 2500 mg/day • Glucophage XR, Glumetza: 2000 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 2000 mg. However, the difference in adjusted mean change in HbA1c between the 1500 and 2000 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 2018 American Diabetes Association (ADA) and 2017 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 ≥ 9% per the ADA (≥ 7.5% 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 ≥ 10% 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 0.9-1.1%.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Farxiga (dapagliflozin)	5 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	300/2000 mg/day
Invokana (canagliflozin)	100 mg PO QD	300 mg/day
Jardiance (empagliflozin)	10 mg PO QD	25 mg/day
Segluromet (ertugliflozin/metformin)	Individualized dose PO BID	15/2000 mg/day
Steglatro (ertugliflozin)	5 mg PO QD	15 mg/day
Synjardy (empagliflozin/metformin)	Individualized dose PO BID	25/2000 mg/day
Xigduo XR (dapagliflozin/metformin)	Individualized dose PO QD	10/2000 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, 50/1000 mg, 150/500 mg, 150/1000 mg
Invokana (canagliflozin)	Tablets: 100 mg, 300 mg
Jardiance (empagliflozin)	Tablets: 10 mg, 25 mg
Segluromet (ertugliflozin/metformin)	Tablets: 2.5/500 mg, 2.5/1000 mg, 7.5/500 mg, 7.5/1000 mg
Steglatro (ertugliflozin)	Tablets: 5 mg, 15 mg
Synjardy (empagliflozin/metformin)	Tablets: 5/500 mg, 5/1000 mg, 12.5/500 mg, 12.5/1000 mg
Xigduo XR (dapagliflozin/metformin)	Tablets: 2.5/1000 mg, 5/500 mg, 5/1000 mg, 10/500 mg, 10/1000 mg

VII. References

1. American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care. 2018; 41(suppl 1): S1-S159.
2. Farxiga Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2017. Available at: www.farxiga.com. Accessed August 27, 2018.

3. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; December 2017. Available at: www.glyxambi.com. Accessed August 27, 2018.
4. Invokamet Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2017. Available at: www.invokamet.com. Accessed August 27, 2018.
5. Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; July 2017. Available at: www.invokana.com. Accessed August 27, 2018.
6. Jardiance Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; December 2017. Available at: www.jardiance.com. Accessed August 27, 2018.
7. Synjardy Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; December 2017. Available at: www.synjardy.com. Accessed August 27, 2018.
8. Xigduo XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2017. Available at: www.xigduoxr.com. Accessed August 27, 2018.
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 – 2017 executive summary. Endocr Pract. 2017; 23(2): 207-238.
11. Steglatro Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017. Available at www.steglatro.com. Accessed August 27, 2018.
12. Segluromet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017. Available at www.segluromet.com. Accessed August 27, 2018.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Changed guidelines to new format. Changed wording from requiring trial and failure of 2000mg 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 2000 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	11.07.17	02.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Allow first line use for members with A1C >= 9% References reviewed and updated		
No signifcant 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: 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).	10.17.18	

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.