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

Reference Number: PA.CP.PMN.14
Effective Date: 01.19
Last Review Date: 01.19
Line of Business: Medicaid

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), empagliflozin (Jardiance®), empagliflozin/linagliptin (Glyxambi®), empagliflozin/metformin (Synjardy®, Synjardy® XR), and ertugliflozin/sitagliptin (Steglujan™).

*Please refer to PA.CP.PST.01 Step Therapy for 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.

Invokana and Jardiance are 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 (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 ≥ 1.5% (12.5 mmol/mol) above their glycemic target, and concurrent use of metformin unless contraindicated or clinically significant adverse effects are experienced;
4. Request meets one of the following (a or b):
   a. Request is for Jardiance, and member has cardiovascular disease;
   b. 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): PA.CP.PMN.53.

**II. Continued Therapy**

**A. Type 2 Diabetes Mellitus (must meet all):**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

   **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): PA.CP.PMN.53.

**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 – PA.CP.PMN.53 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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin</td>
<td>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</td>
<td>Regular-release: 2,550 mg/day</td>
</tr>
<tr>
<td>(Fortamet®, Glucophage®, Glucophage® XR, Glumetza®)</td>
<td>Extended-release:</td>
<td>Extended-release:</td>
</tr>
<tr>
<td></td>
<td>• Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week</td>
<td>• Fortamet: 2,500 mg/day</td>
</tr>
<tr>
<td></td>
<td>• Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week</td>
<td>• Glucophage XR, Glumetza: 2,000 mg/day</td>
</tr>
</tbody>
</table>

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 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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>5 mg PO QD</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Glyxambi (empagliflozin/linagliptin)</td>
<td>One 10/5 mg tablet PO QD</td>
<td>25/5 mg/day</td>
</tr>
<tr>
<td>Invokamet (canagliflozin/metformin)</td>
<td>One 50/500 mg tablet PO BID</td>
<td>300/2,000 mg/day</td>
</tr>
<tr>
<td>Invokamet XR (canagliflozin/metformin)</td>
<td>Two 50/500 mg tablets PO QD</td>
<td>300/2,000 mg/day</td>
</tr>
<tr>
<td>Invokana (canagliflozin)</td>
<td>100 mg PO QD</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Jardiance (empagliflozin)</td>
<td>10 mg PO QD</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Steglujan (ertugliflozin/sitagliptin)</td>
<td>One 5/100 mg tablet PO QD</td>
<td>15/100 mg/day</td>
</tr>
<tr>
<td>Synjardy (empagliflozin/metformin)</td>
<td>Individualized dose PO BID</td>
<td>25/2,000 mg/day</td>
</tr>
<tr>
<td>Synjardy XR (empagliflozin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>25/2,000 mg/day</td>
</tr>
<tr>
<td>Xigduo XR (dapagliflozin/metformin)</td>
<td>Individualized dose PO QD</td>
<td>10/2,000 mg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>Tablets: 5 mg, 10 mg</td>
</tr>
<tr>
<td>Glyxambi (empagliflozin/linagliptin)</td>
<td>Tablets: 10/5 mg, 25/5 mg</td>
</tr>
<tr>
<td>Invokamet (canagliflozin/metformin)</td>
<td>Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg</td>
</tr>
<tr>
<td>Invokamet XR (canagliflozin/metformin)</td>
<td>Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg</td>
</tr>
<tr>
<td>Invokana (canagliflozin)</td>
<td>Tablets: 100 mg, 300 mg</td>
</tr>
<tr>
<td>Jardiance (empagliflozin)</td>
<td>Tablets: 10 mg, 25 mg</td>
</tr>
<tr>
<td>Steglujan (ertugliflozin/sitagliptin)</td>
<td>Tablets: 5/100 mg, 15/100 mg</td>
</tr>
<tr>
<td>Synjardy (empagliflozin/metformin)</td>
<td>Tablets: 5/500 mg, 5/1,000 mg, 12.5/500 mg, 12.5/1,000 mg</td>
</tr>
</tbody>
</table>
**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synjardy XR (empagliflozin/metformin)</td>
<td>Tablets: 5/1,000 mg, 10/1,000 mg, 12.5/1,000 mg, 25/1,000 mg</td>
</tr>
<tr>
<td>Xigduo XR (dapagliflozin/metformin)</td>
<td>Tablets: 2.5/1,000 mg, 5/500 mg, 5/1,000 mg, 10/500 mg, 10/1,000 mg</td>
</tr>
</tbody>
</table>

**VII. References**


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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</thead>
<tbody>
<tr>
<td>1Q 2019 Policy created</td>
<td></td>
<td>01.19</td>
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