Drug Class Monograph

Class: Sodium-Glucose Co-Transporter 2 (SGLT-2) Inhibitors
Drugs: Farxiga (dapagliflozin), Invokamet (canagliflozin/metformin), Invokana (canagliflozin), Jardiance (empagliflozin), Synjardy (empagliflozin/metformin), Xigduo XR (dapagliflozin/metformin ER)

Line of Business: Medi-Cal
Effective Date: February 15, 2017
Revision Date: February 15, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Policy/Criteria:

Step Criteria:

1. Invokamet (canagliflozin/metformin), Invokana (canagliflozin)
   a. Step Therapy: Trial of any metformin containing drug unless contraindicated.

Prior Authorization Criteria:

1. Jardiance (empagliflozin), Synjardy (empagliflozin/metformin)
   a. Confirmed diagnosis of type 2 diabetes mellitus;
   b. Failure or clinically significant adverse effects to metformin;
   c. One of the following:
      i. Documentation of established atherosclerotic cardiovascular disease;
      ii. Failure or clinically significant adverse effects to all of the following:
         1. One of the preferred SGLT-2 inhibitor product (e.g. Invokana);
         2. One additional oral formulary alternatives (e.g. sulfonylurea, Januvia, pioglitazone, etc.).
   d. Documented HbA1c >7% after 3 consecutive months of optimal therapy with the tried alternatives.
2. Other Non-formulary SGLT-2 Inhibitor(s), Non-formulary SGLT-2 inhibitor combination product(s)
   a. Confirmed diagnosis of type 2 diabetes mellitus;
   b. Failure or clinically significant adverse effects to all of the following:
      i. Metformin;
      ii. One of the preferred SGLT-2 inhibitor product (e.g. Invokana);
      iii. One additional oral formulary alternatives (e.g. sulfonylurea, Januvia, pioglitazone, etc.).
   c. Documented HbA1c >7% after 3 consecutive months of optimal therapy with the tried alternatives.

Clinical Justification:

*2016 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm*

- Sodium glucose cotransporter 2 (SGLT-2) inhibitors have a glucosuric effect that results in decreased A1C, weight, and systolic BP.
- In the only SGLT-2 inhibitor cardiovascular outcomes trial reported to date, empagliflozin was associated with significantly lower rates of all-cause and cardiovascular death and lower risk of hospitalization for heart failure.
- SGLT-2 inhibitors are associated with increased risk of mycotic genital infections and slightly increased LDL-C levels, and because of their mechanism of action, they have limited efficacy in patients with an eGFR <45mL/min/1.73 m².
- Dehydration due to increased diuresis may lead to hypotension.
- The incidence of bone fractures in patients taking canagliflozin and dapagliflozin increased in clinical trials.
- Investigations into postmarketing reports of SGLT-2 inhibitor-associated diabetic ketoacidosis (DKA), which has been reported to occur in type 1 diabetes and T2D patients with less than expected hyperglycemia (euglycemic DKA) are ongoing.
- After a thorough review of the evidence during October 2015 meeting, an AACE/ACE Scientific and Clinical Review expert consensus group found that the incidence of DKA is infrequent and recommended no changes in SGLT-2 inhibitor labeling.
2016 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm
Pharmacologic Therapy for Type 2 Diabetes

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.
- Long-term use of metformin may be associated with biochemical vitamin B₁₂ deficiency, and periodic measurement of vitamin B₁₂ levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥10% and/or
blood glucose levels ≥ 300mg/dL.

- If non-insulin monotherapy at maximum tolerated dose not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin.
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost and patient preferences.
- For patients with type 2 diabetes who are not achieving glycemia goals, insulin therapy should not be delayed.
- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

Sodium-Glucose Cotransporter 2 Inhibitors

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2.
- These agents provide modest weight loss and blood pressure reduction.
- There are three FDA-approved agents for use in patients with type 2 diabetes, but there are insufficient data to recommend treatment in type 1 diabetes.
- The FDA recently issued a warning about the risk of ketoacidosis with SGLT2 inhibitors in individuals with type 1 or type 2 diabetes. Patients should stop taking their SGLT2 inhibitors immediately if they have symptoms of ketoacidosis.
- Urinary tract infections leading to urosepsis and pyelonephritis may also occur with SGLT2 inhibitors.

EMPA-REG Cardiovascular Outcomes 2015

- Empagliflozin is the first glucose-lowering agent to show lower CVD event rate and mortality in patients with type 2 diabetes and established CVD. It is unclear at this time whether the cardiovascular benefits are specific to empagliflozin, or represent a class effect of the SGLT-2 inhibitors.
- The primary outcome event (a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) was significantly lower in the empagliflozin group than placebo (10.5% vs. 12.1%; hazard ratio pooled analysis 0.86, 95% CI 0.74-0.99). This outcome was primarily driven by a reduction in CV mortality, as there was insignificant difference for non-fatal myocardial infarction and stroke.

- Health care professionals should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume, chronic kidney insufficiency, congestive heart failure, and taking other medications such as diuretics, blood pressure medicines (ACEi, ARBs), and NSAIDs.
- Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter.
- If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.
- From March 2013, when canagliflozin was approved to October 2015, FDA received reports of 101 confirmable cases of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use. In approximately half of the cases, the events of acute kidney injury occurred within 1 month of starting the drug, and most patients improved after stopping it.

U.S. Food and Drug Administration Drug Safety Communication: Interim Clinical Trial Results Find Increased Risk of Leg and Foot Amputations with Canagliflozin, May 18, 2016

- The FDA alerts the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with the diabetes medicine canagliflozin (Invokana, Invokamet).
- The FDA has not determined whether canagliflozin increases the risk of leg and foot amputations.
- Health care professionals should follow the recommendations in the canagliflozin drug labels. Monitor patients for the signs and symptoms of any new pain or tenderness, sores or ulcers, or infections in their legs or feet.
- In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, amputation occurred about twice as often in patient treated with canagliflozin compared to patients treated with placebo. FDA will continue to evaluate and investigate this safety issue.


- Health care professionals should access for ketoacidosis and urinary tract infections in patients taking SGLT2 inhibitors who present with suggestive symptoms.
- Ketoacidosis associated with the use of SGLT2 inhibitors can occur even if the blood sugar level is not very high. If ketoacidosis is suspected, the SGLT2 inhibitor should be discontinued and treatment instituted promptly.
- Our review of the FDA Adverse Event Reporting System (FAERS) database from March 2013 to May 2015 identified 73 cases of ketoacidosis in patients with type 1 or type 2
diabetes treated with SGLT2 inhibitors. All patients required hospitalization or treatment in an emergency department. In many cases, ketoacidosis was not immediately recognized because the blood glucose levels were below those typically expected for diabetic ketoacidosis.

- 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as urinary tract infection with the SGLT2 inhibitors reported to FAERS from March 2013 through October 2014.
- New Warnings and Precautions to the labels of all SGLT2 inhibitors were added to describe these two safety issues.

**U.S. Food and Drug Administration Drug Safety Communication: FDA Revises Label of Diabetes Drug Canagliflozin (Invokana, Invokamet), September 10, 2015**

- Health care professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin.
- Information about the risk of bone fractures was already in the Adverse Reactions section of the drug label at the time of canagliflozin’s approval.
- Based on updated information about bone fractures from several clinical trials, we revised the drug label and added a new Warning and Precaution. The additional data confirm the finding that fractures occur more frequently with canagliflozin than placebo. Fracture can occur as early as 12 weeks after starting the drug.
- In addition, FDA has added new information about the risk of decreased bone mineral density to the canagliflozin label. Canagliflozin was shown to cause greater loss of bone mineral density at the hip and lower spine than a placebo. This new safety information has been added to the Adverse Reactions section of the drug label.

**Advantages and Disadvantages of SGLT2 Inhibitor:**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>• Effective at all stages of type 2 diabetes</td>
<td>• Limited efficacy in patients with an eGFR &lt;45mL/min/1.73 m²</td>
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<tr>
<td>• No hypoglycemia</td>
<td>• Weak glucose-lowering agent (average A1C reduction 0.4-1.1%)</td>
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<td>• Weight loss (average 2-3 kg)</td>
<td>• Genitourinary infections</td>
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<td>• Lower blood pressure</td>
<td>• Polyuria</td>
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<td>• Associated with lower CVD event rate and mortality in patients with CVD</td>
<td>• Volume depletion, hypotension, dizziness</td>
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<tr>
<td>(empagliflozin)</td>
<td>• UTI leading to urosepsis, pyelonephritis</td>
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<tr>
<td></td>
<td>• Increase LDL-C</td>
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<td>• Increase creatinine (transient)</td>
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<td>• DKA</td>
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<td>• Bladder cancer (dapagliflozin)</td>
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• Decrease bone mineral density (canagliflozin)
• Interim trial results of increased amputation (canagliflozin)

References:


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| 02/15/2017 | • Revised Jardiance and Synjardy criteria:  
  ◦ For patients with established atherosclerotic cardiovascular disease: Failure or clinically significant adverse effects to metformin |