Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
Non-Insulin Diabetes Drugs

Executive Summary

- There are currently three available agents (canagliflozin, dapagliflozin, and empagliflozin) and three fixed-dose combinations (canagliflozin/metformin, dapagliflozin/metformin XR, and empagliflozin/linagliptin).
- Since the SGLT2 inhibitors were first reviewed in May 2013, each has been reviewed individually and all are currently nonformulary.
- Step therapy applies: patients must first try metformin or a sulfonylurea (SU) and a dipeptidyl peptidase-4 (DPP-4) inhibitor.
- There have been no head-to-head studies between any of the SGLT2 inhibitors.
- When used as monotherapy, SGLT2 inhibitors lowered A1c by ~0.4% to 1.3%.
- As part of dual therapy, SGLT2 inhibitors lowered A1c by ~0.5% to 2%.
- As part of triple therapy, SGLT2 inhibitors lowered A1c as low as 0.3% (with sitagliptin and metformin) and as high as 1% [canagliflozin with metformin/SU or thiazolidinediones (TZD)] or (dapagliflozin + insulin +/- oral antidiabetic agents).
- In general, SGLT2 inhibitors decrease triglycerides, increase low-density lipoprotein and high-density lipoprotein, and decrease weight.
- SGLT2 inhibitors consistently provided small but clinically significant decreases in systolic blood pressure (~4-6 mmHg), regardless of monotherapy or adjunctive use.
- SGLT2 inhibitors should be avoided in renal impairment.
- The most common adverse drug reactions are genital mycotic infections and urinary tract infections.
- SGLT2 inhibitors offer another oral option as add-on therapy when other agents no longer provide adequate glycemic control.
- There is a high degree of therapeutic interchangeability between canagliflozin, dapagliflozin, and empagliflozin.

Previous Uniform Formulary Review

The SGLT2 inhibitors were first reviewed in May 2013. Canagliflozin was designated nonformulary. Dapagliflozin was reviewed in May 2014 and empagliflozin was reviewed in February 2015. Both were designated nonformulary. Step therapy applies to the subclass, which requires a trial of metformin or a SU and a preferred DPP-4 inhibitor (i.e., sitagliptin) prior to the use of a SGLT2 inhibitor.

Table 1: Current Formulary Status
Note: Invokamet, Xigduo XR, and Glyxambi have not been reviewed.

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>BCF</th>
<th>UF</th>
<th>NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>None</td>
<td>None</td>
<td>Must try metformin or a SU first AND a DPP-4 inhibitor; 180-day look back</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Sodium-Glucose Co-Transporter 2 Inhibitors Available in the United States

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Brand (Manufacturer)</th>
<th>Strengths</th>
<th>FDA Approval Date</th>
<th>Patent Expiration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Invokana (Janssen)</td>
<td>100 mg, 300 mg</td>
<td>3/29/2013</td>
<td>2024</td>
</tr>
<tr>
<td>Canagliflozin/metformin</td>
<td>Invokamet</td>
<td>50/500 mg; 50/1000 mg 150/500 mg; 150/1000 mg</td>
<td>8/8/2014</td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga (BMS/AstraZeneca)</td>
<td>5 mg,10 mg</td>
<td>1/8/2014</td>
<td>-</td>
</tr>
<tr>
<td>Dapagliflozin/metformin XR</td>
<td>Xigduo XR (BMS/AstraZeneca)</td>
<td>5/500 mg; 5/1000 mg 10/500 mg; 10/1000 mg</td>
<td>10/29/2014</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Jardiance (Boehringer Ingelheim)</td>
<td>10 mg, 25 mg</td>
<td>8/1/2014</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin/linagliptin</td>
<td>Glyxambi (Boehringer Ingelheim)</td>
<td>10/5 mg, 25/5 mg</td>
<td>1/30/15</td>
<td></td>
</tr>
</tbody>
</table>
Indications
All SGLT2 inhibitors are indicated as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).4-6

Efficacy
The safety and efficacy of canagliflozin was studied in a series of nine phase 3, double-blind, randomized, controlled multinational studies enrolling approximately 10,300 patients.1,3-9 The studies varied in length from 18 to 104 weeks and examined canagliflozin in patients with T2DM as monotherapy (with placebo), dual therapy (one with sitagliptin and one with glibenpiride), and as triple therapy (one with sitagliptin, three with placebo). There have also been studies conducted in special populations (one with elderly patients and one in patients with moderate renal impairment). Across all studies, canagliflozin was used in combination with diet and exercise and evaluated against active comparators including metformin, a SU, metformin/SU combination, metformin/TZD combination, and with insulin.1,7-9

Eleven studies with dapagliflozin were included in this review, including four monotherapy studies, six dual therapy studies (four with metformin, one with a TZD, and one with a SU), and two triple therapy studies (one with sitagliptin/metformin and one with insulin plus other oral agents). The studies ranged from 12 to 156 weeks.10-20 Similar active comparators were evaluated in the dapagliflozin studies, which included metformin, a SU, TZD, DPP-4 inhibitor, and insulin.

Eight studies with empagliflozin were included in this review: one monotherapy study, three dual therapy studies (two with metformin and one with a sulfonylurea), three triple therapy studies (one with SU/metformin, one with TZD/metformin, and one with insulin/metformin) and one quadruple therapy study (insulin/metformin/SU). The studies ranged from 24-104 weeks.3,6,21-30 As seen in the canagliflozin and dapagliflozin studies, active comparators included metformin, a SU, TZD, DPP-4 inhibitor, and insulin.

A systematic review found that SGLT2 inhibitors had a favorable effect on HbA1c levels with a mean difference of -0.66% [95% CI, -0.73% to -0.58%] when compared with placebo and an average difference of -0.06% [95% CI, -0.18% to 0.05%] when evaluated against active comparators.31 A reduction in body weight was also shown with a mean difference of 1.8 kg and reductions seen in systolic blood pressure with a mean difference of 4.45 mmHg. Authors concluded there were no clinically significant differences found between the SGLT2 inhibitors in terms of glycemic control.31

Additional Safety Concerns
• There are no major drug interactions reported to date for dapagliflozin and empagliflozin. However, canagliflozin is reported to have decreased effects when used with UGT inducers and may increase the extent of digoxin absorption.4-6
• While a 30-month safety update presented statistics that could not provide a causal relationship between use of dapagliflozin and bladder cancer, labeling does include a warning that dapagliflozin should not be used in patients with a history of bladder cancer.3

References
1. Invokana (canagliflozin). Janssen Pharmaceuticals, Inc. Academy of Managed Care Pharmacy Dossier. April 2015.


**Abbreviations**

The following abbreviations are used in this review:

- **DPP-4** – dipeptidyl peptidase-4
- **SGLT2** – sodium-glucose co-transporter 2 inhibitors
- **SU** – sulfonylurea
- **TZD** – thiazolidinediones
- **T2DM** – type 2 diabetes mellitus