SGLT2 Inhibitors

Description

Invokana (canagliflozin), Invokamet, Invokamet XR (canagliflozin & metformin), Steglatro (ertugliflozin), Steglujan (ertugliflozin & sitagliptin), Segluromet (ertugliflozin & metformin)

Background

Invokana (canagliflozin), Invokamet, Invokamet XR (canagliflozin and metformin), Steglatro (ertugliflozin), Steglujan (ertugliflozin and sitagliptin), and Segluromet (ertugliflozin and metformin) are oral sodium-glucose co-transporter 2 (SGLT2) inhibitors indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. They should not be used to treat type 1 diabetes; in those who have increased ketones in their blood or urine (diabetic ketoacidosis); or in those with severe renal impairment, end stage renal disease, or in patients on dialysis. They work by blocking the reabsorption of glucose by the kidney, increasing glucose excretion, and lowering blood glucose levels in diabetics who have elevated blood glucose levels (1-6).

Regulatory Status

FDA-approved indications for SGLT2 Inhibitors – Invokana, Invokamet, Invokamet XR, Steglatro, Steglujan, and Segluromet: They are sodium-glucose co-transporter 2 (SGLT2) inhibitors indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1-6).

Invokana, Invokamet, and Invokamet XR are also indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1-3).
Invokana is also indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria (1).

**Limitation of Use:**
SGLT2 Inhibitors should not be used for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1-6).

Metformin has a boxed warning for lactic acidosis which can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure (2).

Invokana, Invokamet, and Invokamet XR have boxed warnings for lower limb amputations, most frequently of the toe and midfoot. Before initiating therapy, prescribers must consider factors that may increase the risk of amputations and during therapy monitor patients for ulcers or infections of the lower limbs, and discontinue these medications if they complications occur (1-3).

SGLT2 inhibitors are contraindicated in patients with severe renal impairment, end-stage renal disease (ESRD), or dialysis. SGLT2 inhibitors increase serum creatinine and decrease eGFR. Renal function should be evaluated prior to initiating SGLT2 inhibitor therapy and periodically thereafter (1-6).

Renal function and eGFR have an effect on the SGLT2 inhibitor dosing. Steglatro, Steglujan, and Segluromet should not be initiated if the eGFR is below 60 ml/min/1.73m². Invokana should not be initiated in patients with an eGFR less than 30 mL/min/1.73 m². Invokamet should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m² and should not be continued if the eGFR is less than 30 mL/min/1.73 m². A dose reduction is limited to no more than 50mg twice daily for Invokamet and Invokamet XR, and 100mg once daily for Invokana if the eGFR is between 45 to less than 60 ml/min/1.73m² (1-6).

Safety and effectiveness of SGLT2 inhibitors in patients under 18 years of age have not been established (1-6).

FDA safety review has resulted in adding warnings to the labels of a specific class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors about the risks of too much acid in the blood and of serious urinary tract infections. Both conditions can result in
hospitalization. Health care professionals should assess 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. FDA also identified 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as urinary tract infections with the SGLT2 inhibitors (7).

Off-label and alternative uses of Invokana, Invokamet, Invokamet XR, Steglatro, Steglujan, and Segluromet such as enhancement of weight loss and diabetes prevention are not approved by the FDA.

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

SGLT2 inhibitors may be considered medically necessary in patients 18 years of age and older in adults with type 2 diabetes mellitus and if the conditions indicated below are met.

SGLT2 inhibitors may be considered investigational in patients less than 18 years of age and for all other indications.

Prior-Approval Requirements

Age

18 years of age or older

Diagnosis

Patient must have the following:

Type 2 diabetes mellitus

AND ALL of the following:

1. Inadequate treatment response, intolerance, or contraindication to metformin AND ONE of the drugs from the following drug classes:
   a. Alpha-glucosidase inhibitor
   b. Dipeptidyl peptidase 4 inhibitors (DPP-4)
c. Thiazolidinedione
d. Glucagon-like peptide-1 receptor agonists (GLP-1)

2. Patient must have a HgbA1C greater than 7.0%

3. Patient has an eGFR greater than or equal to ONE of the following:
   a. Patients on Steglatro, Steglujan, and Segluromet: ≥ 60 mL/min/1.73m²
   b. Patients on Invokana 100mg: ≥ 30 mL/min/1.73m²
   c. Patients on Invokana > 100mg: ≥ 60 mL/min/1.73m²
   d. Patients on Invokamet or Invokamet XR 50mg: ≥ 45 mL/min/1.73m²
   e. Patients on Invokamet or Invokamet XR > 50mg: ≥ 60 mL/min/1.73m²

4. NO dual therapy with other SGLT2 inhibitors

5. Patient MUST have tried at least TWO of the preferred products (see Appendix 1) unless the patient has a valid medical exception (e.g. inadequate treatment response, intolerance, contraindication)

AND NOT to be used for the following:
1. Diabetic ketoacidosis (DKA)
2. Prevention of diabetes
3. Exclusively used for weight loss

Prior – Approval Renewal Requirements

Age
18 years of age or older

Diagnosis

Patient must have the following:

Type 2 diabetes mellitus

AND ALL of the following:
1. Condition has improved or stabilized on the therapy
2. NO dual therapy with other SGLT2 inhibitors
3. Patient has an eGFR greater than or equal to ONE of the following:
   a. Patients on Steglatro, Steglujan, and Segluromet: ≥ 60 mL/min/1.73m²
b. Patients on Invokana 100mg: ≥ 30 mL/min/1.73m²

c. Patients on Invokana > 100mg: ≥ 60 mL/min/1.73m²

d. Patients on Invokamet or Invokamet XR 50mg: ≥ 45 mL/min/1.73m²

e. Patients on Invokamet or Invokamet XR > 50mg: ≥ 60 mL/min/1.73m²

4. Patient MUST have tried at least TWO of the preferred products (see Appendix 1) unless the patient has a valid medical exception (e.g. inadequate treatment response, intolerance, contraindication)

AND NOT to be used for the following:

1. Diabetic ketoacidosis (DKA)
2. Prevention of diabetes
3. Exclusively used for weight loss

**Policy Guidelines**

**Pre - PA Allowance**

None

**Prior - Approval Limits**

**Duration** 12 months

**Prior – Approval Renewal Limits**

Same as above

**Rationale**

**Summary**

SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Invokamet, Invokamet XR, Steglatro, Steglujan, and Segluromet are contraindicated in setting of severe renal impairment, ESRD, or dialysis particularly in patients with eGFR less than 45 to 60 mL/min/1.73m². Renal function should be monitored during SGLT2s therapy. SGLT2 Inhibitors should not be used for treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1-6).
Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of SGLT2 inhibitors while maintaining optimal therapeutic outcomes.

References

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>September 2015</td>
<td>New addition to PA</td>
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<tr>
<td>December 2015</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>March 2016</td>
<td>Annual editorial review</td>
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<tr>
<td></td>
<td>Addition of inadequate treatment response, intolerance, or contraindication to one of the following: alpha-glucosidase inhibitor, sulfonylurea, or thiazolidinedione; addition of eGFR’s for the different medications</td>
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<tr>
<td></td>
<td>Changed the wording of weight loss to exclusively used for weight loss</td>
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<tr>
<td></td>
<td>Policy number change from 5.07.19</td>
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<tr>
<td>September 2016</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>October 2016</td>
<td>Addition of Invokamet XR</td>
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<tr>
<td>December 2016</td>
<td>Annual review</td>
</tr>
<tr>
<td>January 2017</td>
<td>Addition of Synjardy XR</td>
</tr>
<tr>
<td>March 2017</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
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<td>Addition of Qtern and the age requirement in the renewal section</td>
</tr>
<tr>
<td>June 2017</td>
<td>Annual editorial review</td>
</tr>
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<td>Addition of dipeptidyl peptidase 4 inhibitors (DPP-4) and glucagon-like peptide-1 receptor agonists (GLP-1) to the tried and failed requirement</td>
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<tr>
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<td>Removal of sulfonylurea from the tried and failed requirement</td>
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<tr>
<td>January 2018</td>
<td>Addition of Steglatro, Steglujan, and Segluromet</td>
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<tr>
<td>March 2018</td>
<td>Annual editorial review Change in initiation criteria from: inadequate treatment response, intolerance, or contraindication to metformin monotherapy, to inadequate treatment response, intolerance, or contraindication to metformin.</td>
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<tr>
<td>June 2018</td>
<td>Annual review and reference update Addition of eGFR requirement to the renewal section and the removal of no severe renal impairment, ESRD, or on dialysis</td>
</tr>
<tr>
<td>November 2018</td>
<td>Annual editorial review and reference update. Updated Invokana, Invokamet, and Invokamet XR indications. Removed Step Edit SGLT2s from policy: Farxiga, Qtern, Jardiance, Glyxambi, Synjardy, Synjardy XR, Xigduo XR</td>
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<tr>
<td>November 2019</td>
<td>Reduced Invokana 100 mg required eGFR from $\geq 45$ to $\geq 30$</td>
</tr>
<tr>
<td>December 2019</td>
<td>Annual review and reference update. Addition of requirement to trial preferred products</td>
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**Keywords**

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 6, 2019 and is effective on January 1, 2020.
### Appendix 1 - List of Preferred SGLT2s

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>dapagliflozin</td>
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<tr>
<td>empagliflozin/metformin</td>
<td>Synjardy XR</td>
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