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5.30.19

Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Endocrine and Metabolic Agents	**Original Policy Date:**	September 18, 2015
Subject:	SGLT2 Inhibitors	**Page:**	1 of 8

Last Review Date: March 12, 2021

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 patients with diabetes 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, Invokamet, and Invokamet XR are 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 (1-3).

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).

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/1.73m^2. Invokana should not be initiated in patients with an eGFR less than 30 mL/min/1.73 m^2, however patients with albuminuria greater than 300 mg/day may continue 100 mg once daily to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure. Invokamet and Invokamet XR should not be continued in patients with eGFR less than 30 mL/min/1.73 m^2. A dose reduction is limited to no more than 50mg twice daily for Invokamet and Invokamet XR if the eGFR is between 30 to less than 60 mL/min/1.73m^2 (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
Metformin, SGLT2 Step Policy, Trijardy XR

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 **OR** patient has albuminuria greater than 300 mg/day
c. Patients on Invokana > 100mg: ≥ 60 mL/min/1.73m²
d. Patients on Invokamet or Invokamet XR 50mg: ≥ 30 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 **OR** patient has albuminuria greater than 300 mg/day
    c. Patients on Invokana > 100mg: ≥ 60 mL/min/1.73m²

   d. Patients on Invokamet or Invokamet XR 50mg: ≥ 30 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. 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

1. Invokana [package insert] Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020.

2. Invokamet [package insert] Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020.
3. Invokamet XR [package insert] Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020.
4. Steglatro [package insert] Whitehouse Station, NJ: Merck & Co., Inc.; January 2020.
5. Steglujan [package insert] Whitehouse Station, NJ: Merck & Co., Inc.; January 2020.
6. Segluromet [package insert] Whitehouse Station, NJ: Merck & Co., Inc.; January 2020.
7. FDA News Release. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. December 4, 2015.

Policy History

Date	Action
September 2015	New addition to PA
December 2015	Annual editorial review and reference update
March 2016	Annual editorial review 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 Changed the wording of weight loss to exclusively used for weight loss Policy number change from 5.07.19
September 2016	Annual editorial review and reference update
October 2016	Addition of Invokamet XR
December 2016	Annual review
January 2017	Addition of Synjardy XR
March 2017	Annual editorial review and reference update Addition of Qtern and the age requirement in the renewal section
June 2017	Annual editorial review Addition of dipeptidyl peptidase 4 inhibitors (DPP-4) and glucagon-like peptide-1 receptor agonists (GLP-1) to the tried and failed requirement Removal of sulfonylurea from the tried and failed requirement
January 2018	Addition of Steglatro, Steglujan, and Segluromet
March 2018	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.
June 2018	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

November 2018	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
November 2019	Reduced Invokana 100 mg required eGFR from ≥ 45 to ≥ 30
December 2019	Annual review and reference update. Addition of requirement to trial preferred products
June 2020	Annual review and reference update
September 2020	Annual review. Revised eGFR limits for Invokana, Invokamet, and Invokamet XR and added the option of albuminuria > 300 mg/day for Invokana 100 mg. Also removed boxed warning statement for lower limb amputation for Invokana, Invokamet, and Invokamet XR
November 2020	Addition of Trijardy XR
January 2021	Removal of Trijardy XR to its own policy
March 2021	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

Appendix 1 - List of Preferred SGLT2s

Generic Name	Brand Name
dapagliflozin	Farxiga
dapagliflozin/metformin	Xigduo XR
dapagliflozin/saxagliptin	Qtern
empagliflozin	Jardiance
empagliflozin/linagliptin	Glyxambi
empagliflozin/metformin	Synjardy
empagliflozin/metformin	Synjardy XR