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# 5.30.019

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**Last Review Date:** December 8, 2023

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## SGLT2 Inhibitors

### Description

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

### Background

Brenzavvy (bexagliflozin), 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 (1-7).

### Regulatory Status

FDA-approved indications for SGLT2 Inhibitors: Brenzavvy, 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 (1-7).

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).

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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 (1-7).

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 (1-7).

Renal function and eGFR have an effect on the SGLT2 inhibitor dosing. Brenzavvy is not recommended in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>. The use of Steglatro, Steglujan, and Segluomet is not recommended in patients with an eGFR is below 45 mL/min/1.73m<sup>2</sup>. Invokana should not be initiated in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>, 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<sup>2</sup>. 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<sup>2</sup> (1-7).

Safety and effectiveness of SGLT2 inhibitors in patients under 18 years of age have not been established (1-7).

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

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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 (8).

Off-label and alternative uses of Brenzavvy, 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

GLP-1 Agonists, Insulin GLP-1 Combinations, Metformin, Mounjaro, 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** if the conditions indicated below are met.

SGLT2 inhibitors may be considered **investigational** 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%

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3. Patient has an eGFR greater than or equal to **ONE** of the following:
  - a. Patients on **Brenzavvy**:  $\geq 30$  mL/min/1.73m<sup>2</sup>
  - b. Patients on **Steglatro**, **Steglujan**, and **Segluromet**:  $\geq 45$  mL/min/1.73m<sup>2</sup>
  - c. Patients on **Invokana 100mg**:  $\geq 30$  mL/min/1.73m<sup>2</sup> **OR** patient has albuminuria greater than 300 mg/day
  - d. Patients on **Invokana > 100mg**:  $\geq 60$  mL/min/1.73m<sup>2</sup>
  - e. Patients on **Invokamet or Invokamet XR 50mg**:  $\geq 30$  mL/min/1.73m<sup>2</sup>
  - f. Patients on **Invokamet or Invokamet XR > 50mg**:  $\geq 60$  mL/min/1.73m<sup>2</sup>
4. **NO** dual therapy with other SGLT2 inhibitors (see Appendix 1)
5. Patient **MUST** have tried at least **TWO** of the preferred products (see Appendix 2) 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 (see Appendix 1)
3. Patient has an eGFR greater than or equal to **ONE** of the following:
  - a. Patients on **Brenzavvy**:  $\geq 30$  mL/min/1.73m<sup>2</sup>
  - b. Patients on **Steglatro**, **Steglujan**, and **Segluromet**:  $\geq 45$  mL/min/1.73m<sup>2</sup>

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- c. Patients on **Invokana 100mg**:  $\geq 30$  mL/min/1.73m<sup>2</sup> **OR** patient has albuminuria greater than 300 mg/day
  - d. Patients on **Invokana > 100mg**:  $\geq 60$  mL/min/1.73m<sup>2</sup>
  - e. Patients on Invokamet or **Invokamet XR 50mg**:  $\geq 30$  mL/min/1.73m<sup>2</sup>
  - f. Patients on Invokamet or **Invokamet XR > 50mg**:  $\geq 60$  mL/min/1.73m<sup>2</sup>
4. Patient **MUST** have tried at least **TWO** of the preferred products (see Appendix 2) 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 (1-7).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of SGLT2 inhibitors while maintaining optimal therapeutic outcomes.

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## 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.; May 2022.
5. Steglujan [package insert] Whitehouse Station, NJ: Merck & Co., Inc.; June 2022.
6. Segluromet [package insert] Whitehouse Station, NJ: Merck & Co., Inc.; May 2022.
7. Brenzavvy [package insert]. Marlborough, MA: TheracosBio, LLC; July 2023.
8. 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<br>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<br>Changed the wording of weight loss to exclusively used for weight loss<br>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<br>Addition of Qtern and the age requirement in the renewal section  |
| June 2017      | Annual editorial review<br>Addition of dipeptidyl peptidase 4 inhibitors (DPP-4) and glucagon-like peptide-1 receptor agonists (GLP-1) to the tried and failed requirement<br>Removal of sulfonylurea from the tried and failed requirement   |
| January 2018   | Addition of Steglatro, Steglujan, and Segluromet  |

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| March 2018     | Annual editorial review<br>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<br>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 $\geq 45$ to $\geq 30$   |
| 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   |
| October 2021   | Revised eGFR limit for Steglatro, Steglujan, and Segluromet to $\geq 45$ mL/min/1.73m <sup>2</sup>  |
| December 2021  | Annual review   |
| September 2022 | Annual review and reference update. Addition of Appendix 1  |
| September 2023 | Annual review. Added Inpefa to Appendix 1   |
| December 2023  | Annual editorial review. Addition of Brenzavvy to policy  |

## Keywords

**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.**

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### Appendix 1 - List of SGLT2 Inhibitors

| Generic Name                        | Brand Name             |
|-------------------------------------|------------------------|
| bexagliflozin                       | Brenzavvy              |
| canagliflozin                       | Invokana               |
| canagliflozin/metformin             | Invokamet/Invokamet XR |
| dapagliflozin                       | Farxiga                |
| dapagliflozin/metformin             | Xigduo XR              |
| dapagliflozin/saxagliptin           | Qtern                  |
| empagliflozin                       | Jardiance              |
| empagliflozin/linagliptin           | Glyxambi               |
| empagliflozin/linagliptin/metformin | Trijardy XR            |
| empagliflozin/metformin             | Synjardy/Synjardy XR   |
| ertugliflozin                       | Steglatro              |
| ertugliflozin/metformin             | Segluromet             |
| ertugliflozin/sitagliptin           | Steglujan              |
| sotagliflozin                       | Inpefa                 |

### Appendix 2 - List of Preferred SGLT2 Inhibitors

| 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 |