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PHARMACY POLICY – 5.01.646

SGLT2 Inhibitors

Effective Date:	Jan. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 10, 2024	5.01.569 Pharmacotherapy of Type I and Type II Diabetes Mellitus
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
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Introduction

Metabolism refers to how the body converts the energy supplied by food into energy the body can use. Diabetes is a disease of the metabolic system. Diabetes involves production of and response to insulin. Insulin is a hormone produced by certain cells in the pancreas called beta cells. These cells regulate the amount of glucose (sugar) in the blood. There are two types of diabetes: type 1 and type 2. In type 2 diabetes, people can still make insulin, but their bodies don't respond well to it. This is known as insulin resistance. Type 2 diabetes can be diagnosed at any age and can be affected and modified by a number of factors, such diet and exercise and other health conditions. This policy discusses when each type of sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

This policy contains separate criteria to be used based on the member's formulary. Please check the member Plan booklet or member ID card for coverage and click the links below to navigate to the appropriate section:

Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage

Section 2: Individual/Small Group/Student ISHIP Metallic Formulary Plans (Rx Plan M1, M2, and M4)

The following section applies to non-Metallic formulary plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and plans with no pharmacy benefit coverage only. Please refer to the member plan booklet or member ID card.

Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY	
Drug	**Medical Necessity**
First-line SGLT2 Inhibitors	
Farxiga (dapagliflozin)	**Farxiga (dapagliflozin) may be considered medically necessary for the treatment of type 2 diabetes when ALL the following criteria are met:** • The individual is diagnosed with type 2 diabetes (**Related Information**) **AND** • Has tried and had an inadequate response or intolerance to metformin unless contraindicated **Farxiga (dapagliflozin) may be considered medically necessary for the treatment of chronic kidney disease when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Receiving concurrent therapy with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), unless ACEi and ARBs are not tolerated

Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY	
Drug	**Medical Necessity**
	Farxiga (dapagliflozin) may be considered medically necessary when ALL the following criteria are met: • The individual is aged 18 years or older **AND** • The individual has a diagnosis of chronic heart failure (NYHA Class II to IV) **AND** • Has an estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73m^2 or greater to initiate therapy **AND** • Use is prescribed by or in consultation with a cardiologist or a cardiac care specialist
Jardiance (empagliflozin)	**Jardiance (empagliflozin) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:** • The individual is diagnosed with type 2 diabetes (**Related Information**) **AND** • Has tried and had an inadequate response or intolerance to metformin unless contraindicated **Jardiance (empagliflozin) may be considered medically necessary for the treatment of chronic kidney disease when ALL the following criteria are met:** • The individual is aged 18 years or older **AND**

Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY	
Drug	**Medical Necessity**
	• Receiving concurrent therapy with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), unless ACEi and ARBs are not tolerated **Jardiance (empagliflozin) may be considered medically necessary when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • The individual has a diagnosis of chronic heart failure (NYHA Class II to IV) **AND** • Has an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73m^2 or greater to initiate therapy **AND** • Use is prescribed by or in consultation with a cardiologist or a cardiac care specialist
• **Synjardy (empagliflozin-metformin)** • **Synjardy XR (empagliflozin-metformin extended-release)** • **Xigduo XR (dapagliflozin-metformin extended-release)**	**Synjardy (empagliflozin-metformin), Synjardy XR (empagliflozin-metformin extended-release), and Xigduo XR (dapagliflozin-metformin extended-release) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:** • The individual is diagnosed with type 2 diabetes (**Related Information**) **AND** • Has tried and had an inadequate response or intolerance to metformin unless contraindicated
Second-line SGLT2 Inhibitors	
• **Brand bexagliflozin** • **Brenzavvy (bexagliflozin)** • **Brand dapagliflozin**	**Brand bexagliflozin, Brenzavvy (bexagliflozin), brand dapagliflozin, brand dapagliflozin-metformin, Invokana (canagliflozin), Invokamet (canagliflozin-metformin),**

Section 1: Non-Metallic Formulary Plans (Rx Plan A1, A2, B3, B4, C4, E1, E3, E4, F1, and G3) and Plans with No Pharmacy Benefit Coverage ONLY	
Drug	**Medical Necessity**

• **Brand dapagliflozin-metformin**
• **Invokana (canagliflozin)**
• **Invokamet (canagliflozin-metformin)**
• **Invokamet XR (canagliflozin-metformin extended-release)**
• **Steglatro (ertugliflozin)**
• **Segluromet (ertugliflozin-metformin)**
	Invokamet XR (canagliflozin-metformin extended-release), Steglatro (ertugliflozin), and Segluromet (ertugliflozin-metformin) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:
	• The individual is diagnosed with type 2 diabetes (**Related Information**)
	
	AND
	• Has tried and had an inadequate response or intolerance to metformin unless contraindicated
	
	AND
	• Has tried and had an inadequate response or intolerance to TWO of the following:
	  ○ Farxiga (dapagliflozin)
	  ○ Jardiance (empagliflozin)
	  ○ Synjardy (empagliflozin-metformin)
	  ○ Synjardy XR (empagliflozin-metformin extended-release)
	  ○ Xigduo XR (dapagliflozin-metformin extended-release)

The following section applies to Individual and Small Group Metallic Formulary Plans (Rx Plan M1, M2, and M4) only. Please refer to the member's Plan.

Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY	
Drug	**Medical Necessity**
First-line SGLT2 Inhibitors	
Jardiance (empagliflozin)	**Jardiance (empagliflozin) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:** • The individual is diagnosed with type 2 diabetes (**Related Information**)

Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY	
Drug	**Medical Necessity**
	AND • Has tried and had an inadequate response or intolerance to metformin unless contraindicated **Jardiance (empagliflozin) may be considered medically necessary for the treatment of chronic kidney disease when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Receiving concurrent therapy with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), unless ACEi and ARBs are not tolerated **Jardiance (empagliflozin) may be considered medically necessary when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • The individual has a diagnosis of chronic heart failure (NYHA Class II to IV) **AND** • Has an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73m^2 or greater to initiate therapy **AND** • Use is prescribed by or in consultation with a cardiologist or a cardiac care specialist
• **Synjardy (empagliflozin-metformin)** • **Synjardy XR (empagliflozin-metformin extended-release)**	**Synjardy (empagliflozin-metformin) and Synjardy XR (empagliflozin-metformin extended-release) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:**

Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY	
Drug	**Medical Necessity**
	• The individual is diagnosed with type 2 diabetes (**Related Information**) **AND** • Has tried and had an inadequate response or intolerance to metformin unless contraindicated
Second-line SGLT2 Inhibitors	

• **Brand bexagliflozin**
• **Brenzavvy (bexagliflozin)**
• **Brand dapagliflozin**
• **Brand dapagliflozin-metformin**
• **Invokana (canagliflozin)**
• **Invokamet (canagliflozin-metformin)**
• **Invokamet XR (canagliflozin-metformin extended-release)**
• **Steglatro (ertugliflozin)**
• **Segluromet (ertugliflozin-metformin)**
• **Xigduo XR (dapagliflozin-metformin extended-release)**
	Brand bexagliflozin, Brenzavvy (bexagliflozin), brand dapagliflozin, brand dapagliflozin-metformin, Invokana (canagliflozin), Invokamet (canagliflozin-metformin), Invokamet XR (canagliflozin-metformin extended-release), Steglatro (ertugliflozin), Segluromet (ertugliflozin-metformin), and Xigduo XR (dapagliflozin-metformin extended-release) may be considered medically necessary for the treatment of type 2 diabetes when all the following criteria are met:
	• The individual is diagnosed with type 2 diabetes (**Related Information**)
	
	AND
	• Has tried and had an inadequate response or intolerance to metformin unless contraindicated
	
	AND
	• Has tried and had an inadequate response or intolerance to one of the following:
	  ○ Jardiance (empagliflozin)
	  ○ Synjardy (empagliflozin-metformin)
	  ○ Synjardy XR (empagliflozin-metformin extended-release)

Farxiga (dapagliflozin)	**Farxiga (dapagliflozin) may be considered medically necessary for the treatment of type 2 diabetes when ALL the following criteria are met:** • The individual is diagnosed with type 2 diabetes (**Related Information**) **AND**

Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY	
Drug	**Medical Necessity**
	• Has tried and had an inadequate response or intolerance to metformin unless contraindicated **AND** • Has tried and had an inadequate response or intolerance to one of the following: ○ Jardiance (empagliflozin) ○ Synjardy (empagliflozin-metformin) ○ Synjardy XR (empagliflozin-metformin extended-release) **Farxiga (dapagliflozin) may be considered medically necessary for the treatment of chronic kidney disease when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • Receiving concurrent therapy with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), unless ACEi and ARBs are not tolerated **AND** • Has tried and had an inadequate response or intolerance to Jardiance (empagliflozin) **Farxiga (dapagliflozin) may be considered medically necessary when ALL the following criteria are met:** • The individual is aged 18 years or older **AND** • The individual has a diagnosis of chronic heart failure (NYHA Class II to IV) **AND**

Section 2: Individual/Small Group/Student ISHIP METALLIC Formulary Plans (Rx Plan M1, M2, and M4) ONLY	
Drug	**Medical Necessity**
	• Has an estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73m^2 or greater to initiate therapy **AND** • Has tried and had an inadequate response or intolerance to Jardiance (empagliflozin) **AND** • Use is prescribed by or in consultation with a cardiologist or a cardiac care specialist

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of the drugs for conditions not listed in this policy are considered investigational.**

Drug	Not Medically Necessary
As listed	**All other uses of the drugs for approved conditions listed in this policy are considered not medically necessary.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in this policy may be approved for up to 3 years.**
Re-authorization criteria	**Future re-authorization of all drugs listed in the policy may be approved for up to 3 years as long as the medical necessity criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

N/A

Related Information

Benefit Application

All drugs addressed in this policy are managed through the pharmacy benefit.

Criteria for Diagnosis of Diabetes in Nonpregnant Individuals[1]

Criteria for Diagnosis of Diabetes in Nonpregnant Individuals
A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., A1C and FPG) or at two different time points.

Staging of Type 1 Diabetes[1]

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic Criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100-125 mg/dL (5.6-6.9 mmol/L) • 2-h PG 140-199 mg/dL (7.8-11.0 mmol/L) • A1C 5.7-6.4% (39-47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by **standard criteria**

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials.

Evidence Review

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are oral agents indicated to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. A couple of SGLT2 drugs, Farxiga (dapagliflozin) and Jardiance (empagliflozin), are also approved for non-diabetes specific indications. Jardiance is approved for the treatment of individuals with a diagnosis of chronic heart failure while Farxiga is approved for the treatment of individuals with a diagnosis of chronic heart failure and for the treatment of chronic kidney disease. SGLT2 inhibitors decrease glucose reabsorption in the proximal nephron and increase urinary glucose excretion. The mechanism of action of SGLT2 inhibitors is not dependent on insulin.

Large, well-designed, long-term trials and meta-analyses have shown SGLT2 inhibitors decrease HbA1c in comparison to placebo (-0.7 to -1.1%). SGLT2 inhibitors have been extensively studied in dual and triple therapy regimens, typically as add-on agents to metformin, SUs, DPP4s, and

TZDs. Since the last review, new data has become available supporting the use of dapagliflozin in triple therapy regimens. Additionally, longer duration trials to 104 weeks have been published indicating continued effectiveness. Trials comparing SGLT2 inhibitors to other classes of agents have found no difference in effectiveness in comparison with metformin. However, available data conflicts about the efficacy of SGLT2 inhibitors in comparison to other classes (SU, TZDs, and DPP4s) with some data indicating superiority and others non-inferiority. In addition, trials with SGLT2 inhibitors are associated with decreased body weight and BP. Adverse events with SGLT2 inhibitors include genital mycotic infections, UTIs, and, less commonly, volume depletion and renal-related effects. The FDA has recently issued two safety warnings for the class, concerning an increased risk of DKA across the class as well as increased incidence of upper extremity, low- trauma fractures with canagliflozin. Further research is needed to fully define these effects as well as the CV effects of the class. Cost effectiveness studies in the US setting comparing SGLT2 inhibitors to other classes of agents for T2DM are not available and drug costs remain high.

EMPA-REG: CV Outcomes Trial Summary

The goal of the trial was to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care (such as, lifestyle, risk reduction with antihypertensive treatment, statins, aspirin, and metformin), on cardiovascular (CV) morbidity and mortality in individuals with T2DM and high risk of CV events. This was a randomized (1:1:1 to empagliflozin 10mg, 25mg, and placebo), double-blind, placebo-controlled, international CV outcomes trial. The total number of participants was 7,028. This was an industry-sponsored trial.

Key findings included:

- The primary outcome, CV death, nonfatal MI, or stroke for empagliflozin vs. placebo: 10.5% vs. 12.1%, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.74 to 0.99, $p<0.001$ for non-inferiority; $p=0.04$ for superiority.
- For CV death: 3.7% vs. 5.9%, $p<0.001$
- All MI: 4.8% vs. 5.4%, $p=0.23$
- All stroke: 3.5% vs. 3.0, $p=0.26$
- Reduced risk of composite cardiovascular events (NNT=63/3 years) and all cause death (NNT=38/3years). The 10mg daily dose provided almost the same benefit as the 25mg dose.

Benefit realized despite A1C not reaching target (A1C=7.8%). Mean change was about ≤0.6%.

- Increased risk of genital infections in both males (NNH=29/3 years) and females (NNH=14/3 years). Urosepsis, although rare, was also increased with empagliflozin (~0.4% vs. 0.1%). Serious Adverse Events (SAE) were less with empagliflozin than placebo (NNT=24). A
- Empagliflozin also lowered systolic blood pressure (SBP) by 3 to 4 mm Hg, and diastolic blood pressure (DBP) by 1 to 2 mm Hg.
- Weight was also noted to decrease by about 1 to 2 kg, which was more than in the placebo group.
- The average A1C achieved in the empagliflozin group was 7.8%.

For details on secondary outcomes (all-cause mortality, congestive heart failure (CHF) hospitalization, CV death, all cause hospitalization, coronary revascularization, A1C at 12 weeks for 10mg dose, A1C at 12 weeks for 25mg dose, confirmed hypoglycemic event, and urinary tract infection rates), and for renal outcomes (incident or worsening nephropathy, doubling of serum creatinine, progression to macroalbuminuria, and initiation of renal replacement therapy), please refer to the American College of Cardiology article, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Individuals- EMPA-REG Outcome. Available at: **https://www.acc.org/latest-in-cardiology/clinical-trials/2015/09/17/10/11/empa-reg-outcome**. (Accessed November 28, 2024).

The results of this trial demonstrate that empagliflozin is superior to placebo in improving glycemic control and reducing CV events in individuals with type 2 diabetes and established cardiovascular disease. The fact that CV safety is thought to be established in this trial is an important factor in light of the prior serious safety concerns involving rosiglitazone. However, the mechanism for this benefit is still unknown (and may be due to non-glucose related mechanism).

References

1. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S20–S42. https://doi.org/10.2337/dc24-S002
2. Package insert for Farxiga (dapagliflozin). AstraZeneca, Wilmington, DE. Revised October 2024.

3. Package insert for Jardiance (empagliflozin). Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT. Revised September 2023.
4. Package insert for Invokana (canagliflozin). Janssen Pharmaceuticals, Inc., Titusville, NJ. Revised August 2024.
5. Package insert for Steglatro (ertugliflozin). Merck Sharp & Dohme LLC, Rahway, NJ. Revised June 2024.

History

Date	Comments
01/01/25	New policy, approved December 10, 2024. Moved Farxiga, Jardiance, Brenzavvy, brand bexagliflozin, brand dapagliflozin, Invokana, Steglatro, Synjardy, Synjardy XR, Xigduo XR, brand dapagliflozin-metformin, Invokamet, Invokamet XR, and Segluromet from Policy 5.01.569 to 5.01.646 with no changes to Section 1 (non-Metallic formulary plans and plans with no pharmacy benefit coverage) coverage criteria. Section 2 addresses individual/small group/student ISHIP Metallic formulary plans with hyperlinks to aid navigation which lists separate coverage criteria for Metallic (individual/small group/student ISHIP plans) formulary members for the following drugs: Farxiga, Jardiance, Brenzavvy, brand bexagliflozin, brand dapagliflozin, Invokana, Steglatro, Synjardy, Synjardy XR, Xigduo XR, brand dapagliflozin-metformin, Invokamet, Invokamet XR, and Segluromet. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.