Clinical Policy: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

Reference Number: OR.CP.PMN.14
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Line of Business: Medicaid – Trillium Oregon Health Plan

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following agents contain a sodium-glucose co-transporter 2 (SGLT2) inhibitor and require prior authorization: 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/sitagliptin (Steglujan™), and sotagliflozin (Inpefa™).

FDA Approved Indication(s)
Other than Inpefa, SGLT2 inhibitors are indicated as adjunct to diet and exercise to improve glycemic control in adults (*all SGLT2 inhibitors*) and pediatric patients aged 10 years and older (*Jardiance and Synjardy only*) with type 2 diabetes mellitus.

Dapagliflozin-, canagliflozin-, and empagliflozin-containing products are also indicated in adult patients with type 2 diabetes mellitus and established cardiovascular (CV) disease (or multiple CV risk factors [*dapagliflozin only*]) to:
- Reduce the risk of hospitalization for heart failure (HF) (*dapagliflozin*)
- Reduce the risk of major adverse CV events: CV death, nonfatal myocardial infarction, and nonfatal stroke (*canagliflozin*)
- Reduce the risk of CV death (*empagliflozin*)

Canagliflozin-containing products are additionally indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF (HHF) in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day.

Farxiga is additionally indicated to:
- Reduce the risk of CV death, HHF, and urgent HF visit in adults with HF
- Reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end stage kidney disease cardiovascular death, and HHF in adults with chronic kidney disease (CKD) at risk of progression

Jardiance is additionally indicated to reduce the risk of CV death and HHF in adults with HF.

Empagliflozin, when used as a component of Synjardy or Synjardy XR, is additionally indicated in adults with type 2 diabetes mellitus to reduce the risk of cardiovascular death and HHF in adults with HF.

Inpefa is indicated to reduce the risk of CV death, HHF, and urgent HF visit in adults with:
- HF
- Type 2 diabetes mellitus, CKD, and other CV risk factors

Limitation(s) of use:
- Other than Inpefa, SGLT2 inhibitors should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. SGLT2 inhibitors may increase the risk of diabetic ketoacidosis.
- Farxiga is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. Farxiga is likely to be ineffective in this setting based upon its mechanism of action.
- Farxiga and Xigduo XR are not recommended for the treatment of CKD in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease. Farxiga and Xigduo XR are not expected to be effective in these populations.
- Jardiance and Glyxambi are not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. They are likely to be ineffective in this setting based upon their mechanism of action.
- Steglujan has not been studied in patients with a history of pancreatitis.
- Because of the metformin component, the use of Xigduo XR is limited to adults with type 2 diabetes mellitus for all indications.
- Because of the metformin component, Synjardy and Synjardy XR are not recommended for use in patients with heart failure without type 2 diabetes mellitus.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Trillium Community Health Plan that SGLT2 inhibitors are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Type 2 Diabetes Mellitus (must meet all)**:**

1. Diagnosis of type 2 diabetes mellitus;
2. Request is for an SGLT2 inhibitor other than Inpefa;*
   **If request is for Inpefa, please refer to criteria set I.B below for heart failure and I.D below for other indications.*
3. Age is one of the following (a or b):
   a. Jardiance or Synjardy: ≥10 years;
   b. All other SGLT2 inhibitors: ≥ 18 years;
4. Member meets one of the following (a, b, c, or d):

a. Failure of ≥ 3 consecutive months of metformin, unless contraindicated or clinically significant adverse effects are experienced;
b. For antidiabetic medication-naïve members, requested agent is approvable if intended for concurrent use with metformin due to HbA1c ≥ 8.5% (drawn within the past 3 months);
c. History of ≥ 3 consecutive months insulin use and at high ASCVD risk (age ≥ 55 years with coronary carotid, lower extremity artery stenosis > 50%, or LVH);
d. Request is for an agent with proven CV benefit (dapagliflozin-, canagliflozin-, empagliflozin-containing products), and member has established ASCVD, indicators of high ASCVD risk (*see Appendix D*), HF, or CKD;

5. If age ≥ 18 years: Request meets one of the following (a, b, c or d):
   a. Failure of ≥ 3 consecutive months of Steglatro or Segluromet, unless clinically significant adverse effects are experienced or both are contraindicated;
   b. Member has established CV disease (e.g., ASCVD or HF) or diabetic nephropathy/CKD, and request is for a formulary dapagliflozin- or empagliflozin-containing product, unless clinically significant adverse effects are experienced or all are contraindicated;
   c. Member has multiple risk factors for CV disease (*see Appendix D)*, and request is for a canagliflozin-, dapagliflozin- or empagliflozin-containing product, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

Approval duration: 12 months

B. Heart Failure (must meet all):
1. Diagnosis of HF;
2. Request is for Farxiga, Inpefa, or Jardiance;*
   **If request is for Synjardy, Synjardy XR, or Xigduo XR, please refer to criteria set I.A above.*
3. Prescribed by or in consultation with a cardiologist;
4. Age ≥ 18 years;
5. If request is for Farxiga or Jardiance, HF is NYHA Class II, III, or IV;
6. If request is for Inpefa, both of the following (a and b):
   a. Member has a diagnosis of type 2 diabetes mellitus;
   b. Member was recently (within the last 30 days) hospitalized or had an urgent HF visit to an emergency department, HF unit, or infusion centers due to intravascular volume overload (examples of clinical signs and symptoms of congestion include but are not limited to: dyspnea, jugular venous distention, pitting edema in lower extremities (> 1+), rales heard on auscultation, radiographic pulmonary congestion);
7. Member does not have a diagnosis of type 1 diabetes mellitus;
8. Dose does not exceed (a or b):
   a. Farxiga or Jardiance (i and ii):
      i. 10 mg per day;
      ii. 1 tablet per day;
   b. Inpefa (i and ii):

i. 400 mg per day;
ii. 1 tablet per day.

Approval duration: 12 months

C. Chronic Kidney Disease (must meet all)**:**
1. Diagnosis of CKD;
2. Request is for Farxiga;*
   **If request is for Xigduo XR, please refer to criteria set I.A above. If request is for Inpefa, please refer to criteria set I.D below.*
3. Age ≥ 18 years;
4. Both of the following (a and b):
   a. eGFR between 25 and 75 mL/min/1.73 m^2;
   b. Urine albumin creatinine ratio (UACR) ≥ 200 mg/g;
5. Member does not have a diagnosis of type 1 diabetes mellitus or polycystic kidney disease;
6. Member has not received immunosuppressive therapy for the treatment of kidney disease in the past 6 months;
7. Member is currently receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker at maximally tolerated doses for ≥4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated;
8. Dose does not exceed (a and b):
   a. 10 mg per day;
   b. 1 tablet per day.

Approval duration: 12 months

D. Requests for Inpefa for Diagnoses Other Than Heart Failure (must meet all):
1. Diagnosis of both of the following (a and b):
   a. Type 2 diabetes mellitus;
   b. CKD with eGFR between 25 and 60 mL/min/1.73 m^2;
2. Request is for Inpefa;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. If age 18 to 54 years: Member has at least one major CV risk factor (*see Appendix E);*
   b. If age ≥ 55 years: Member has at least two minor CV risk factors (*see Appendix E*);
5. Dose does not exceed (a and b):
   a. 400 mg per day;
   b. 1 tablet per day.

Approval duration: 12 months

E. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Type 2 Diabetes Mellitus (must meet all):

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Request is for an SGLT2 inhibitor other than Inpefa;*
   **If request is for Inpefa, please refer to criteria set II.B below for heart failure and II.D below for other indications.*
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose (*see Section V*).

Approval duration: 12 months

B. Heart Failure (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Farxiga, Inpefa, or Jardiance for HF and has received this medication for at least 30 days;
2. Request is for Farxiga, Inpefa, or Jardiance;*
   **If request is for Synjardy, Synjardy XR, or Xigduo XR, please refer to criteria set II.A above.*
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed (a or b):
   a. Farxiga or Jardiance (i and ii):
      i. 10 mg per day;
      ii. 1 tablet per day;
   b. Inpefa (i and ii):
      i. 400 mg per day;
      ii. 1 tablet per day.

Approval duration: 12 months

C. Chronic Kidney Disease (must meet all):

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

2. Request is for Farxiga;*
   **If request is for Xigduo XR, please refer to criteria set II.A above. If request is for Inpefa, please refer to criteria set II.D below.*
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed (a and b):
   a. 10 mg per day;
   b. 1 tablet per day.

Approval duration: 12 months

D. Requests for Inpefa for Diagnoses Other Than Heart Failure (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Request is for Inpefa;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed (a and b):
   a. 400 mg per day;
   b. 1 tablet per day.

Approval duration: 12 months

E. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the PDL (Medicaid), the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

B. Inpefa: type 1 diabetes.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AACE: American Association of Clinical Endocrinologists
ACE: American College of Endocrinology
ADA: American Diabetes Association
ASCVD: atherosclerotic cardiovascular disease
CAC: coronary artery calcium
CKD: chronic kidney disease
CV: cardiovascular
DPP-4: dipeptidyl peptidase-4
eGFR: estimated glomerular filtration rate
ER: extended-release
FDA: Food and Drug Administration
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin
HF: heart failure
HHF: hospitalization for heart failure
IR: immediate-release
SGLT2: sodium-glucose co-transporter 2
UACR: urine albumin creatinine ratio

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
metformin (Fortamet®, Glucophage®, Glucophage® XR, Glumetza®)	Regular-release (Glucophage): 500 mg PO BID or 850 mg PO QD; increase as needed in increments of 500 mg/week or 850 mg every 2 weeks Extended-release: • Fortamet, Glumetza: 1,000 mg PO QD; increase as needed in increments of 500 mg/week • Glucophage XR: 500 mg PO QD; increase as needed in increments of 500 mg/week	Regular-release: 2,550 mg/day Extended-release: 2,000 mg/day
Segluromet (ertugliflozin/ metformin)	Individualized dose PO BID	15/2,000 mg/day
Steglatro (ertugliflozin)	5 mg PO QD	15 mg/day
Angiotensin Converting Enzyme Inhibitors		
captopril (Capoten®)	Initially, 6.25 mg PO 3 times daily, then increase to 50 mg PO 3 times daily if tolerated.	450 mg/day
enalapril (Vasotec®, Epaned®)	Initially, 2.5 mg PO twice daily, then increase to 10 to 20 mg PO twice daily if tolerated.	40 mg/day
fosinopril (Monopril®)	Initially, 5 to 10 mg PO once daily, then increase to 40 mg/day if tolerated.	80 mg/day
lisinopril (Prinivil®, Zestril®, Qbrelis®)	Initially, 2.5 to 5 mg PO once daily, then increase to 20 to 40 mg/day if tolerated.	80 mg/day
perindopril (Aceon®)	Initially, 4 mg PO once daily for 2 weeks, then increase to 8 mg PO once daily if tolerated.	16 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
quinapril (Accupril®)	Initially, 5 mg PO twice daily, then increase to 20 mg PO twice daily of tolerated.	80 mg/day
ramipril (Altace®)	Initially, 2.5 mg PO once daily. Gradually titrate to 5 mg/day PO, then increase if tolerated to the target dosage of 10 mg/day PO, given in 1 to 2 divided doses.	20 mg/day
trandolapril (Mavik®)	Initially, 1 mg PO once daily, then increase to 4 mg/day if tolerated.	8 mg/day
Angiotensin Receptor Blockers		
candesartan (Atacand®)	Initially, 4 to 8 mg PO once daily, then increase to 32 mg/day if tolerated.	32 mg/day
losartan (Cozaar®)	Initially, 25 to 50 mg PO once daily, then increase to 50 to 150 mg/day if tolerated.	100 mg/day
telmisartan (Micardis®)	80 mg PO once daily	80 mg/day
valsartan (Diovan®)	Initially, 20 to 40 mg PO twice daily, then increase dose to 160 mg PO twice daily if tolerated.	320 mg/day
Angiotensin Receptor-Neprilysin Inhibitor/Angiotensin Receptor Blocker		
Entresto® (sacubitril/valsartan)	The recommended starting dose is 49/51 mg (sacubitril/valsartan) PO BID. Double the dose after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) BID, as tolerated by the patient.	194/206 mg/day
Beta Blockers Recommended for HF		
bisoprolol (Zebeta®)	Initially, 1.25 mg PO QD for 48 hours, then 2.5 mg QD for the first month, then 5 mg QD.	10 mg/day
carvedilol (Coreg®, Coreg CR®)	Immediate-release: Initially, 3.125 mg PO BID for 2 weeks. Dosage may be subsequently increased to 6.25, 12.5, and then 25 mg PO BID over successive intervals of at least 2 weeks. Extended-release: Initially, 10 mg PO QD for 2 weeks. Dosage may be subsequently increased to 20, 40, and then 80 mg PO QD over successive intervals of at least 2 weeks.	Immediate-release: 100 mg/day Extended-release: 80 mg/day
metoprolol succinate extended release (Toprol XL®)	25 mg PO QD for 2 weeks in patients with NYHA class II HF, or 12.5 mg PO QD in patients with more severe HF. Double the dose every 2 weeks as tolerated, up to the target dosage of 200 mg PO QD.	200 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - History of serious hypersensitivity reaction to the requested drug product
  - Moderate to severe renal impairment*, end-stage renal disease, or dialysis (all products except Inpefa)
    **Minimum degree of renal impairment varies per agent; refer to individual prescribing information*
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis (*metformin-containing products only*)
- Boxed warning(s): lactic acidosis (*metformin-containing products only*).

Appendix D: General Information

- Per the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines:
  - Metformin is recommended for all patients with type 2 diabetes. It is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Monotherapy is recommended for most patients; however:
    - Starting with dual therapy (i.e., metformin plus another agent, such as a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitor, SGLT2 inhibitor, glucagon-like peptide 1 [GLP-1] receptor agonist, or basal insulin) may be considered for patients with baseline HbA1c ≥ 1.5% above their target. According to the ADA, a reasonable HbA1c target for many non-pregnant adults is < 7% (≤ 6.5% per the AACE/ACE).
    - Starting with combination therapy with insulin may be considered for patients with baseline HbA1c > 10% or if symptoms of hyperglycemia are present.
    - For patients with established ASCVD or indicators of high ASCVD risk, HF, or CKD, use of an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular benefit is recommended as part of the glucose-lowering regimen independent of HbA1c and metformin use.
  - If the target HbA1c is not achieved after approximately 3 months of monotherapy, dual therapy should be initiated. If dual therapy is inadequate after 3 months, triple therapy should be initiated. Finally, if triple therapy fails to bring a patient to goal, combination therapy with insulin should be initiated. Each non-insulin agent added to initial therapy can lower HbA1c by 0.7-1%.
- Although Invokana is currently the only SGLT2 inhibitor with a labeled indication for diabetic nephropathy, Farxiga and Jardiance have also demonstrated renal protective effects. The ADA guidelines recommend SGLT2 inhibitors be considered when treating type 2 diabetic patients with renal concerns, noting that Farxiga, Jardiance, and Invokana all confer renal benefit, with no preference for one over the other;
  - Farxiga DECLARE-TIMI 58: The cardiorenal secondary composite outcome (sustained decline of at least 40% in eGFR to less than 60 mL/min/1.73 m2, end stage renal disease (ESRD), or death from renal or CV causes) was significantly reduced with Farxiga compared to placebo (HR 0.76, 95% CI 0.67-0.87; p < 0.0001); excluding death from CV causes, the HR for the renal-specific outcome was 0.53 (95% CI 0.43-0.66; p < 0.0001). There was a 46% reduction in sustained decline in

eGFR by at least 40% to less than 60 mL/min/1.73 m2 (120 [1.4% vs 221 [2.6%]; HR 0.54 [95% CI 0.43-0.67]; p < 0.0001). The risk of ESRD or renal death was also lower in the Farxiga group than in the placebo group (11 [0.1%] vs 27 [0.3%]; HR 0.41 [95% CI 0.20-0.82]; p = 0.012).
    - Jardiance EMPA-REG Outcome: Analysis of secondary outcomes yielded a reduction of risk for incident of or worsening nephropathy (HR 0.61 [95% CI 0.53-0.70]), progression to urine albumin to creatinine ratio (UACR) > 300 mg/g (HR 0.62 [95% CI 0.54-0.72]), composite consisting doubling of serum creatinine, initiation of renal replacement therapy, and death from ESRD (HR 0.54 [95% CI 0.40-0.75]).
- Examples of CV risk factors may include but are not limited to: dyslipidemia, hypertension, obesity, a family history of premature coronary disease, and smoking.
- According to the ADA, ASCVD includes coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin. Indicators of high ASCVD risk are age ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis > 50%; left ventricular hypertrophy; retinopathy; and other end organ damage.
- Although Farxiga and Invokana are the only SGLT2 inhibitors with labeled indications for reducing the risk of HHF, Jardiance has also been shown to reduce the risk of HHF. The ADA guidelines acknowledge Farxiga along with Jardiance and Invokana as agents which reduce the risk of HHF, without a preference for one agent over the other. Any of the three can be used in T2DM patients with established HF; however, the guidelines recommend only Jardiance or Invokana for patients with established ASCVD.
    - Jardiance EMPA-REG Outcome, patients with established ASCVD: The primary outcome (composite of death from CV causes, nonfatal MI, or non-fatal stroke) was reduced with Jardiance compared to placebo (HR 0.86, 95% CI 0.74 – 0.99; p = 0.04). Analysis of secondary outcomes yielded a reduction in hospitalization for heart failure when treated with Jardiance compared to placebo (HR 0.65, 95% CI 0.50 – 0.85; p = 0.002).
    - Invokana CANVAS Program, patients with established ASCVD or multiple ASCVD risk factors: The primary outcome (composite of death from CV causes, nonfatal MI or nonfatal stroke) was reduced with Invokana compared to placebo (HR 0.86, 95% CI 0.75 – 0.97; p = 0.02). Analysis of secondary outcomes yielded a reduction in hospitalization for heart failure when treated with Invokana compared to placebo (HR 0.67, 95% CI 0.52 – 0.87).
- In August 2020, the FDA removed the boxed warning regarding the risk of leg and foot amputations from the canagliflozin prescribing information. Although the risk is still present (and continues to be described in the Warnings and Precautions section of the prescribing information), the FDA notes the significantly enhanced benefit of canagliflozin (e.g., effects in heart and kidney disease) relative to said risk, which safety information from recent trials suggest is lower than previously described.

Appendix E: CV Risk Factors per Inpefa SCORED Pivotal Study

- Major CV risk factors:
    - Hospitalization for HF during previous 2 years
    - Ejection fraction ≤ 40% documented within the past year by previous imaging modality, or documented with screening echocardiogram

- Left ventricular hypertrophy by either electrocardiogram or echocardiogram
- Coronary artery calcium (CAC) score ≥ 300 Agatston Units
- N-terminal pro-B-type natriuretic peptide ≥ 400 pg/mL (47 pmol/L)
- High-sensitivity troponin T > 15.0 pg/mL for men and > 10.0 pg/mL for women
- High-sensitivity C-reactive protein > 3 mg/L (28.6 nmol/L)
- UACR ≥ 300 mg/g (34 mg/mmol)

- Minor CV risk factors:
  - Body mass index ≥ 35 kg/m^2
  - Dyslipidemia despite maximally-tolerated statin therapy: LDL > 130 mg/dL or HDL < 40 mg/dL for men or < 50 mg/dL for women
  - Currently smoking tobacco
  - CAC score > 100 and < 300 Agatston Units
  - UACR ≥ 30 mg/g and < 300 mg/g
  - Systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg despite antihypertensive therapy
  - Family history of premature coronary heart disease (defined as myocardial infarction or coronary revascularization procedure) in a first-degree male relative < 55 years or first-degree female relative < 65 years

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Brenzavvy (bexagliflozin)	20 mg PO QD	20 mg/day
Farxiga (dapagliflozin)	Diabetes: 5 mg PO QD HFrEF, CKD: 10 mg PO QD	10 mg/day
Glyxambi (empagliflozin/linagliptin)	One 10/5 mg tablet PO QD	25/5 mg/day
Inpefa (sotagliflozin)	200 mg PO QD; titrate to 400 mg PO QD as tolerated	400 mg/day
Invokamet (canagliflozin/metformin)	One 50/500 mg tablet PO BID	300/2,000 mg/day
Invokamet XR (canagliflozin/metformin)	Two 50/500 mg tablets PO QD	300/2,000 mg/day
Invokana (canagliflozin)	100 mg PO QD	300 mg/day
Jardiance (empagliflozin)	10 mg PO QD	Diabetes: 25 mg/day HF: 10 mg/day
Qtern (dapagliflozin/saxagliptin)	One 5/5 mg tablet PO QD	10/5 mg/day
Steglujan (ertugliflozin/sitagliptin)	One 5/100 mg tablet PO QD	15/100 mg/day
Synjardy (empagliflozin/metformin)	Individualized dose PO BID	25/2,000 mg/day
Synjardy XR (empagliflozin/metformin)	Individualized dose PO QD	25/2,000 mg/day
Trijardy XR (empagliflozin/linagliptin/ metformin)	Individualized dose PO QD	25/5/2,000 mg/day
Xigduo XR (dapagliflozin/metformin)	Individualized dose PO QD	10/2,000 mg/day

VI. Product Availability

Drug Name	Availability
Brenzavvy (bexagliflozin)	Tablets: 20 mg
Farxiga (dapagliflozin)	Tablets: 5 mg, 10 mg
Glyxambi (empagliflozin/linagliptin)	Tablets: 10/5 mg, 25/5 mg
Inpefa (sotagliflozin)	Tablets: 200 mg, 400 mg
Invokamet (canagliflozin/metformin)	Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg
Invokamet XR (canagliflozin/metformin)	Tablets: 50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg
Invokana (canagliflozin)	Tablets: 100 mg, 300 mg
Jardiance (empagliflozin)	Tablets: 10 mg, 25 mg
Qtern (dapagliflozin/saxagliptin)	Tablets: 5/5 mg, 10/5 mg
Steglujan (ertugliflozin/sitagliptin)	Tablets: 5/100 mg, 15/100 mg
Synjardy (empagliflozin/metformin)	Tablets: 5/500 mg, 5/1,000 mg, 12.5/500 mg, 12.5/1,000 mg
Synjardy XR (empagliflozin/metformin)	Tablets: 5/1,000 mg, 10/1,000 mg, 12.5/1,000 mg, 25/1,000 mg
Trijardy XR (empagliflozin/linagliptin/ metformin)	Tablets: 5/2.5/1,000 mg, 10/5/1,000 mg, 12.5/2.5/1,000 mg, 25/5/1,000 mg
Xigduo XR (dapagliflozin/metformin)	Tablets: 2.5/1,000 mg, 5/500 mg, 5/1,000 mg, 10/500 mg, 10/1,000 mg

VII. References

1. American Diabetes Association. Standards of medical care in diabetes—2022. Diabetes Care. 2022; 45(suppl 1): S1-S264. Updated May 2022. Accessed October 26, 2022.
2. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: Developing a diabetes mellitus comprehensive care plan – 2022 update. Endocrine Practice. 2022; 28(10): 923-1049.
3. Brenzavvy Prescribing Information. Marlborough, MA: TheracosBio, LLC; January 2023. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2023/214373s000lbl.pdf. Accessed February 2, 2023.
4. Farxiga Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2023. Available at: www.farxiga.com. Accessed May 26, 2023.
5. Qtern Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2022. Available at: www.qtern.com. Accessed October 27, 2022.
6. Xigduo XR Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2022. Available at: www.xigduoxr.com. Accessed October 27, 2022.
7. Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020. Available at: www.invokana.com. Accessed October 27, 2022.
8. Invokamet/Invokamet XR Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; August 2020. Available at: www.invokamet.com. Accessed October 27, 2022.

9. Jardiance Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2022. Available at: www.jardiance.com. Accessed October 27, 2022.
10. Glyxambi Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2022. Available at: www.glyxambi.com. Accessed October 27, 2022.
11. Synjardy Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; June 2023. Available at: www.synjardy.com. Accessed June 27, 2023.
12. Synjardy XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; February 2023. Available at: www.synjardyxr.com. Accessed February 23, 2023.
13. Trijardy XR Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2022. Available at: www.trijardy.com. Accessed October 27, 2022.
14. Steglatro Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; October 2022. Available at: www.steglatro.com. Accessed October 27, 2022.
15. Segluromet Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; October 2022. Available at: www.segluromet.com. Accessed October 27, 2022.
16. Steglujan Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; October 2022. Available at: www.steglujan.com. Accessed October 27, 2022.
17. Inpefa Prescribing Information. The Woodlands, TX; Lexicon Pharmaceuticals, Inc.; May 2023. Available at: www.inpefa.com. Accessed June 19, 2023.
18. Patorno E, Pawar A, Franklin JM, et al. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. Circulation AHA; 2019 Jun 18;139(25):2822-2830. doi: 10.1161/CIRCULATIONAHA.118.039177
19. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644-657. DOI: 10.1056/NEJMoa1611925
20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128. DOI:10.1056/NEJMoa1504720
21. Yancy C, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Am Coll Cardiol. 2017 Aug, 70 (6) 776-803.
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney inter., Suppl. 2013; 3: 1–150.
23. Maddox TM, Januzzi JL, Allen LA, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb; 77(6): 772-810.
24. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895-e1032.
25. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes Association (ADA) and Kidney Disease:

Improving Global Outcomes (KDIGO). Diabetes Care. 2022; dci220027. Available at: https://diabetesjournals.org/care/article/doi/10.2337/dci22-0027/147614/Diabetes-Management-in-Chronic-Kidney-Disease-A. Accessed November 3, 2022.
26. Bhatt DL, Szarek M, Pitt B et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021; 384: 129-139.
27. Bhatt DL, Szarek M, Steg G et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021; 384: 117-128.

Reviews, Revisions, and Approvals	Date	Plan Approval Date
Policy created: adapted from previously approved policy TCHP.PHAR.2002 Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors. Added CKD indication to policy.	09.21.21	
Removed requirement to have four or more weeks of standard HF or CKD drug therapy in I.B.7 & I.B.7 per P&T Committee.	10.21.21	10.21.21
1Q 2022 annual review: no significant changes; removed Qternmet XR as it is no longer on market; references reviewed and updated.	12.21.21	01.06.22
For HFrEF, removed requirement for prior use of standard HF therapy as SGLT2 inhibitors are now a recommended first line therapy per 2022 AHA/ACC/HFSA guidelines.	06.15.22	07.07.22
1Q 2023 annual review: added bypass of metformin for members with ASCVD, indicators of high ASCVD risk, HF, or CKD per ADA guidelines; references reviewed and updated.	12.14.22	01.05.23
RT4: added Brenzavvy to policy; updated FDA Approved Indication(s) section with Synjardy/Synjardy XR's updated indication in heart failure for the empagliflozin component and new limitation of use per revised PI; updated HF criteria per Farxiga's revised indication for HF regardless of ejection fraction; added Inpefa to policy; updated diabetes criteria per Jardiance and Synjardy's pediatric extensions for age ≥ 10 years; removed Steglatro and Segluromet from policy as PA requirement to be removed 10.1.23.	08.2.23	09.19.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.