STEP THERAPY CRITERIA

CATEGORY **ANTIDIABETIC AGENTS**

DRUG CLASS
BRAND NAME*
(generic)

AMYLIN ANALOG:

SYMLINPEN
(pramlintide acetate)

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITOR:

BRENZAVVY
(bexagliflozin)

FARXIGA
(dapagliflozin)

INVOKANA
(canagliflozin)

JARDIANCE
(empagliflozin)

STEGLATRO
(ertugliflozin)

SGLT2 INHIBITOR / METFORMIN:

INVOKAMET
(canagliflozin / metformin HCl)

INVOKAMET XR
(canagliflozin /metformin HCl extended-release)

SEGLUROMET
(ertugliflozin / metformin HCl)

SYNJARDY
(empagliflozin / metformin HCl)

SYNJARDY XR
(empagliflozin / metformin HCl extended-release)

XIGDUO XR

(dapagliflozin / metformin HCl)

SGLT2 INHIBITOR / DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITOR:
GLYXAMBI
(empagliflozin / linagliptin)

QTERN
(dapagliflozin / saxagliptin)

STEGLUJAN
(ertugliflozin / sitagliptin)

SGLT2 INHIBITOR / DPP4 INHIBITOR / METFORMIN:
TRIJARDY XR
(empagliflozin / linagliptin / metformin HCl extended-release)

LONG ACTING INSULIN/GLP-1 RECEPTOR AGONIST:
SOLIQUA
(insulin glargine / lixisenatide injection)

XULTOPHY
(insulin degludec / liraglutide injection)

Status: Client Requested Criteria
Type: Logic with Step Therapy;
Post Step Therapy Prior Authorization ***Ref # C25493-D***

**Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA APPROVED INDICATIONS

AMYLIN ANALOG:

SymlinPen

SymlinPen is indicated as an adjunctive treatment in patients with type 1 or type 2 diabetes who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

SGLT2 INHIBITOR:

Brenzavvy

Brenzavvy is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

Brenzavvy is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Farxiga

Farxiga (dapagliflozin) is indicated:

- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

- To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

- Farxiga is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients
- 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 is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. Farxiga is not expected to be effective in these populations.

Invokana

Invokana (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use

Invokana is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Invokana is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73m^2. Invokana is likely to be ineffective in this setting based upon its mechanism of action.

Jardiance

Jardiance is indicated:

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
- to reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.
- as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

Limitation of Use

Jardiance is not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Jardiance is not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m2. Jardiance is likely to be ineffective in this setting based upon its mechanism of action.

Jardiance is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease. Jardiance is not expected to be effective in these populations.

Steglatro

Steglatro is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

SGLT2 INHIBITOR / METFORMIN:
Invokamet, Invokamet XR

Invokamet and Invokamet XR are a combination of canagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
Canagliflozin is indicated to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.
Limitations of Use
Invokamet/Invokamet XR is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Segluromet

Segluromet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use
Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Synjardy, Synjardy XR

Synjardy is a combination of empagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.
Synjardy XR is a combination of empagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Empagliflozin, when used as a component of Synjardy/Synjardy XR, is indicated in adults with type 2 diabetes mellitus to reduce the risk of:

- Cardiovascular death in adults with established cardiovascular disease.
- Cardiovascular death and hospitalization for heart failure in adults with heart failure.

Limitation of Use

- Synjardy/Synjardy XR are not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Because of the metformin component, Synjardy/Synjardy XR is not recommended for use in patients with heart failure without type 2 diabetes mellitus.

Xigduo XR

Xigduo XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Dapagliflozin is indicated to reduce:

- the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.
- the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- the risk of sustained estimated glomerular filtration rate decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitation of Use

- Xigduo XR is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Because of the metformin component, the use of Xigduo XR is limited to adults with type 2 diabetes for all indications.
- Xigduo XR is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. Xigduo XR is not expected to be effective in these populations.

SGLT2 INHIBITOR / DPP-4 INHIBITOR:
Glyxambi

Glyxambi is a combination of empagliflozin and linagliptin indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
Limitations of Use
Glyxambi is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
Glyxambi has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using Glyxambi.
Glyxambi is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 ml/min/1.73m2. Glyxambi is likely to be ineffective in this setting based upon its mechanism of action.

Qtern

Qtern is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use
Qtern is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Steglujan

Steglujan is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use

- Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Steglujan.

SGLT2 INHIBITOR / DPP-4 INHIBITOR / METFORMIN:

Trijardy XR

Trijardy XR is a combination of empagliflozin, linagliptin, and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
Limitations of Use
Trijardy XR is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
Trijardy XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using Trijardy XR.

LONG ACTING INSULIN / GLP-1 RECEPTOR AGONIST:

Soliqua

Soliqua 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use:

- Soliqua 100/33 has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Soliqua 100/33 is not recommended for use in combination with any other product containing a GLP-1 receptor agonist.
- Soliqua 100/33 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Soliqua 100/33 has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.
- Soliqua 100/33 has not been studied in combination with prandial insulin.

Xultophy

Xultophy 100/3.6 is a combination of insulin degludec and liraglutide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitations of Use:

- Xultophy 100/3.6 is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans.
- Xultophy 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist.
- Xultophy 100/3.6 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Xultophy 100/3.6 has not been studied in combination with prandial insulin.

SCREEN OUT LOGIC*
**Include Rx and OTC products unless otherwise stated.*

If the patient has filled a prescription for at least a 30-day supply of Entresto (sacubitril/valsartan) within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested sodium-glucose cotransporter 2 (SGLT2) inhibitor or SGLT2 inhibitor combination drug will be paid under that prescription benefit.

If the patient does not meet the initial screen out logic or is requesting a drug under this criteria that is not an SGLT2 inhibitor or SGLT2 inhibitor combination drug, then the claim will proceed to the initial step therapy criteria outlined in this policy.

INITIAL STEP THERAPY*
**Include Rx and OTC products unless otherwise stated.*

INITIAL STEP THERAPY For AMYLIN ANALOGS (SymlinPen):
If the patient has filled a prescription for at least a 30-day supply of a rapid-acting insulin or short-acting insulin or pre-mixed insulin [e.g., insulin aspart (Novolog), insulin glulisine (Apidra), insulin lispro (Humalog), insulin regular R (Afrezza, Humulin R, Novolin R)] within the past 120 days under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the claim will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

INITIAL STEP THERAPY For ALL OTHER TARGET DRUGS:
If the patient has filled a prescription for at least a 30-day supply of metformin within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the claim will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA
The requested drug will be covered with prior authorization when the following criteria are met:

- The patient has a diagnosis of type 2 diabetes mellitus **AND**
  - The patient has NOT been receiving a stable maintenance dose of the requested drug for at least 3 months **AND**
    - The patient experienced an inadequate treatment response, intolerance, or has a contraindication to metformin

    OR
    - The patient requires combination therapy AND has an A1C of 7.5 percent or greater

    OR

        - The request is for Farxiga (dapagliflozin), Invokana (canagliflozin), or Jardiance (empagliflozin) AND the patient has established cardiovascular disease

      OR

        - The request is for Invokana (canagliflozin) AND the patient has diabetic nephropathy with albuminuria greater than 300 mg per day

      OR

        - The request is for Farxiga (dapagliflozin) AND the patient has multiple cardiovascular risk factors

      OR

        - The request is for Farxiga (dapagliflozin) or Jardiance (empagliflozin) **AND**
          - The patient has a diagnosis of heart failure

      OR

        - The request is for Farxiga (dapagliflozin) or Jardiance (empagliflozin) **AND**
          - The patient has chronic kidney disease at risk of progression

    OR

    - The patient has been receiving a stable maintenance dose of the requested drug for at least 3 months **AND**
        - The patient has demonstrated a reduction in A1C since starting this therapy

      OR

        - The request is for Farxiga (dapagliflozin), Invokana (canagliflozin), or Jardiance (empagliflozin) AND the patient has established cardiovascular disease

      OR

        - The request is for Invokana (canagliflozin) AND the patient has diabetic nephropathy with albuminuria greater than 300 mg per day

      OR

        - The request is for Farxiga (dapagliflozin) AND the patient has multiple cardiovascular risk factors

      OR

        - The request is for Farxiga (dapagliflozin) or Jardiance (empagliflozin) **AND**
          - The patient has a diagnosis of heart failure

      OR

        - The request is for Farxiga (dapagliflozin) or Jardiance (empagliflozin) **AND**
          - The patient has chronic kidney disease at risk of progression

OR

- The request is for SymlinPen (pramlintide acetate) AND the patient has a diagnosis of type 1 or type 2 diabetes mellitus **AND**
    - The patient has NOT been receiving a stable maintenance dose of the requested drug for at least 3 months **AND**
        - The patient has failed to achieve desired glucose control despite receiving optimal insulin therapy, including mealtime insulin

    OR

    - The patient has been receiving a stable maintenance dose of the requested drug for at least 3 months **AND**
        - The patient has demonstrated a reduction in A1C since starting this therapy

OR

- The request is for Farxiga (dapagliflozin) **AND**
    - The patient has a diagnosis of heart failure

    OR

    - The patient has chronic kidney disease at risk of progression

OR

- The request is for Jardiance (empagliflozin) **AND**
    - The patient has a diagnosis of heart failure

    OR

    - The patient has chronic kidney disease at risk of progression

RATIONALE

If the patient has filled a prescription for at least a 30-day supply of Entresto (sacubitril/valsartan) within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested sodium-glucose cotransporter 2 (SGLT2) inhibitor or SGLT2 inhibitor combination drug will be paid under that prescription benefit. If the patient does not meet the initial screen out logic or is requesting a drug under this criteria that is not an SGLT2 inhibitor or SGLT2 inhibitor combination drug, then the claim will proceed to the initial step therapy criteria outlined in this policy.

For Amylin Analogs (SymlinPen), if the patient has filled a prescription for at least a 30-day supply of a rapid-acting insulin or short-acting insulin or premixed insulin [e.g., insulin aspart (Novolog), insulin glulisine (Apidra), insulin lispro (Humalog), insulin regular R (Afrezza, Humulin R, Novolin R)] within the past 120 days under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit.

For all other target drugs, if the patient has filled a prescription for at least a 30-day supply of metformin within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit.

If the patient does not meet the initial step therapy criteria, then prior authorization is required.

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines.

REFERENCES

1. Brenzavvy [package insert]. Marlborough, MA: TherascoBio, LLC.; January 2023.
2. Farxiga [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2023.
3. Glyxambi [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2022.
4. Invokamet, Invokamet XR [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; October 2022.
5. Invokana [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; October 2022.
6. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; September 2023.
7. Qtern [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2022.
8. Segluromet [package insert]. Rahway, NJ: Merck Sharpe & Dohme LLC.; October 2022.
9. Soliqua [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC; June 2022.
10. Steglatro [package insert]. Rahway, NJ: Merck Sharpe & Dohme LLC.; October 2022.
11. Steglujan [package insert]. Rahway, NJ: Merck Sharpe & Dohme LLC.; October 2022.
12. SymlinPen [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2019.
13. Synjardy, Synjardy XR [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; June 2023.
14. Trijardy XR [package Insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; October 2022.
15. Xigduo XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2022.
16. Xultophy [package insert]. Plainsboro, NJ: Novo Nordisk U.S. LLC; June 2022.
17. Lexicomp Online, AHFS DI (Adult and Pediatric) Online. Waltham, MA: UpToDate, Inc.; 2023. https://online.lexi.com. Accessed April 4, 2023.
18. Micromedex (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: 04/04/2023).
19. 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 28 (2022) 923-1049.
20. Davies MJ, Aroda VR, Collins BS, et. al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45(11):2753-2786.
21. El Sayed NA, Aleppo G, Aroda VR et. al. American Diabetes Association, Standards of Care in Diabetes – 2023. Diabetes Care 2023;46(Suppl. 1):S1-S291.

22. 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. J Am Coll Cardiol. 2022;79:e263-e421.
23. Heerspink HJL, Bergur VS, Correa-Rotter R, et al. for the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020;383:1436-46.
24. Alfego D, Ennis J, Gillespie B et. al. Chronic Kidney Disease Testing Among At-Risk Adults in the U.S. Remains Low: Real-World Evidence From a National Laboratory Database. Diabetes Care 2021;44(9):2025-2032.

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