STEP THERAPY CRITERIA

CATEGORY **ANTIDIABETIC AGENTS**

DRUG CLASS
BRAND NAME
(generic)

AMYLIN ANALOG:
SYMLIN/SYMLINPEN
(pramlintide acetate)

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST (GLP-1):
ADLYXIN
(lixisenatide)

BYDUREON
(exenatide extended-release)

BYETTA
(exenatide)

OZEMPIC
(semaglutide)

TANZEUM
(albiglutide)

TRULICITY
(dulaglutide)

VICTOZA
(liraglutide)

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR (SGLT2):
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 INHIBITOR (DPP-4):
GLYXAMBI
(empagliflozin / linagliptin)

QTERN
(dapagliflozin / saxagliptin)

STEGLUJAN
(ertugliflozin / sitagliptin)

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

XULTOPHY
(insulin degludec / liraglutide injection)

Status: CVS Caremark Criteria
Type: Initial Step Therapy; Post Step Therapy Prior Authorization

POLICY

FDA APPROVED INDICATIONS

AMYLIN ANALOG:

Symlin/SymlinPen

Symlin/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.

GLP-1 RECEPTOR AGONIST:

Adlyxin

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

Limitations of Use

- Adlyxin has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Adlyxin is not a substitute for insulin. Adlyxin is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- The concurrent use of Adlyxin with short acting insulin has not been studied and is not recommended.

Adlyxin has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

Bydureon

Bydureon is an extended-release formulation of exenatide, administered as an injection once every 7 days (weekly).

Type 2 Diabetes Mellitus

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

Important Limitations of Use

- Bydureon 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 rat thyroid C-cell tumor findings to humans. Prescribe Bydureon only to patients for whom the potential benefits are considered to outweigh the potential risk. Bydureon 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 rat thyroid C-cell tumor findings to humans. Prescribe Bydureon only to patients for whom the potential benefits are considered to outweigh the potential risks.
- Bydureon is not a substitute for insulin. Bydureon should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of Bydureon with insulin has not been studied and cannot be recommended.
- Bydureon and Byetta (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.
- Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Bydureon 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 pancreatitis while using Bydureon. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

Byetta

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

Important Limitations of Use

- Byetta is not a substitute for insulin. Byetta should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of Byetta with prandial insulin has not been studied and cannot be recommended.
- Based on postmarketing data Byetta has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Byetta 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 pancreatitis while using Byetta. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

Ozempic

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

Limitations of Use

- Ozempic is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans.
- Ozempic has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Ozempic is not a substitute for insulin. Ozempic is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

Tanzeum

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

Limitations of Use

- Tanzeum is not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe Tanzeum only to patients for whom the potential benefits are considered to outweigh the potential risk.
- Tanzeum has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Tanzeum is not indicated in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. Tanzeum is not a substitute for insulin in these patients.
- Tanzeum has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of Tanzeum is not recommended in patients with pre-existing severe gastrointestinal disease.
- Tanzeum has not been studied in combination with prandial insulin.

Trulicity

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

Limitations of Use

- Trulicity is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans. Prescribe Trulicity only to patients for whom the potential benefits outweigh the potential risk.
- Trulicity has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Trulicity should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Trulicity is not a substitute for insulin.
- Trulicity has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of Trulicity is not recommended in patients with pre-existing severe gastrointestinal disease.

Victoza

Victoza 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, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease

Important Limitations of Use

- Victoza is not a substitute for insulin. Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.
- The concurrent use of Victoza and prandial insulin has not been studied.

SGLT2 INHIBITOR:

Farxiga

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

Limitation of Use

Farxiga is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Invokana

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

Limitation of Use

Invokana is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Jardiance

Jardiance 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 cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease

Limitation of Use

Jardiance is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

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

Steglatro is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

SGLT2 INHIBITOR / METFORMIN:

Invokamet

Invokamet (canagliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both canagliflozin and metformin is appropriate.

Limitations of Use

Invokamet is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Invokamet XR

Invokamet XR (canagliflozin and metformin hydrochloride extended release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.

Limitations of Use

Invokamet XR is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Segluromet

Segluromet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin.

Limitations of Use

Segluromet is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Synjardy

Synjardy is a combination of empagliflozin and metformin hydrochloride indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of Synjardy on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitation of Use

Synjardy is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Synjardy XR

Synjardy XR is a combination of empagliflozin and metformin hydrochloride indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of Synjardy XR on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitation of Use

Synjardy XR is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Xigduo XR

Xigduo XR (dapagliflozin and metformin HCl extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

Limitation of Use
Xigduo XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

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 when treatment with both empagliflozin and linagliptin is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of Glyxambi on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use

- Glyxambi is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- 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.

Qtern

Qtern (dapagliflozin and saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin.

Limitations of Use

Qtern is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

Steglujan

Steglujan is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.

Limitations of Use

Steglujan is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Steglujan 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.

LONG ACTING INSULIN / GLP-1 AGONIST:

Soliqua

Soliqua 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 inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

Limitations of Use

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

Xultophy

Xultophy 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 inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).

Limitations of Use

- Xultophy is not recommended as first line therapy for patients who have inadequate glycemic control control on diet and exercise because of uncertain relevance of the rodent C-cell tumor findings to humans
- Xultophy has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

- Xultophy is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist.
- Xultophy is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Xultophy has not been studied in combination with prandial insulin.

INITIAL STEP THERAPY For AMYLIN ANALOGS (Symlin/SymlinPen):
If the patient has filled a prescription for 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 Symlin/SymlinPen will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the system 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 COMBINATION LONG ACTING INSULIN / GLP-1 RECEPTOR AGONISTS:
If the patient has filled a prescription for a 30 day supply of metformin AND long acting insulin [e.g. insulin glargine (Lantus, Toujeo), insulin detemir (Levemir), insulin degludec (Tresiba)] or a GLP-1 receptor agonist [e.g. Tanzeum (albiglutide), Trulicity (dulaglutide), Victoza (liraglutide)] 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 system 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 GLP-1 RECEPTOR AGONISTS, SGLT2 INHIBITORS, and COMBINATIONS (excluding Amylin Analogs and Long Acting Insulin/GLP-1 receptor agonists):
If the patient has filled a prescription for 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 system 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 been receiving the requested drug for at least 3 months AND has demonstrated a reduction in A1c (hemoglobin A1c) since starting this therapy

OR
- The request is for Amylin Analogs (Symlin/SymlinPen) for a patient with a diagnosis of diabetes mellitus AND has failed to achieve desired glucose control despite receiving optimal insulin therapy, including mealtime insulin

OR
- The request is for GLP-1 (glucagon-like peptide-1) Receptor Agonists, SGLT2 (sodium-glucose cotransporter 2) Inhibitors, or Combinations for a patient with a diagnosis of type 2 diabetes mellitus
  AND
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to metformin
    AND
  - If the request is for Soliqua (insulin glargine/lixisenatide) or Xultophy (insulin degludec/liraglutide), the patient has experienced inadequate treatment control on basal insulin or GLP-1 Agonist treatment
    OR
  - The patient requires combination therapy AND has an A1c (hemoglobin A1c) of 7.5 percent or greater
    OR
  - The request is for Jardiance (empagliflozin) or Victoza (liraglutide) for a patient who has established cardiovascular disease

REFERENCES
1. Adlyxin [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; July 2016.

2. Bydureon [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; March 2017.
3. Byetta [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2015.
4. Farxiga [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; March 2017.
5. Glyxambi [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; March 2017.
6. Invokana [package insert]. Titusville, New Jersey: Janssen Pharmaceuticals, Inc.; February 2017.
7. Invokamet [package insert]. Titusville, New Jersey: Janssen Pharmaceuticals, Inc.; March 2017.
8. Invokamet XR [package insert]; Titusville, New Jersey: Janssen Pharmaceuticals, Inc.; February 2017.
9. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; December 2016.
10. Qtern [package insert]. Wilmington, Delaware: AstraZeneca Pharmaceuticals LP; February 2017.
11. Soliqua [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; November 2016.
12. Symlin/SymlinPen [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2016.
13. Synjardy [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; May 2017.
14. Synjardy XR [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; December 2016.
15. Tanzeum [package insert]. Wilmington, DE: GlaxoSmithKline LLC; September 2016.
16. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2017.
17. Victoza [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; August 2017.
18. Xigduo XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; March 2017.
19. Xultophy [package insert]. Plainsboro, NJ: Novo Nordisk U.S. LLC; November 2016.
20. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed July 2017.
21. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed July 2017.
22. Standards of Medical Care in Diabetes-2017: American Diabetes Association (ADA). *Diabetes Care* January 2017;40(Supplement1).
23. Garber A, Barzilay J, Abrahamson M, et al. American Association of Clinical Endocrinologists' Comprehensive Diabetes Management Algorithm 2017. *Endocr Pract.* 2017; 23 (2):207-238.
24. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical Practice Guidelines for developing a diabetes mellitus comprehensive care plan*. Endocr Pract*. 2015;21(Suppl 1):1-87.
25. Ozempic [package insert]. Plainsboro, NJ: Novo-Nordisk Inc.; December 2017.
26. Segluromet [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; December, 2017.
27. Steglatro [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; December, 2017.
28. Steglujan [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; December, 2017.

