STEP THERAPY CRITERIA

CATEGORY **ANTIDIABETIC AGENTS**

DRUG CLASS
BRAND NAME*
(generic)

AMYLIN ANALOG:

SYMLINPEN
(pramlintide acetate)

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

ADLYXIN
(lixisenatide)

BYDUREON
(exenatide extended-release)

BYDUREON BCISE
(exenatide extended-release)

BYETTA
(exenatide)

OZEMPIC
(semaglutide)

RYBELSUS
(semaglutide)

TANZEUM
(albiglutide)

TRULICITY
(dulaglutide)

VICTOZA
(liraglutide)

SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITOR:

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:

QTERNMET XR
(dapagliflozin / saxagliptin / metformin HCl extended-release)

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: CVS Caremark Criteria
Type: Initial Step Therapy; Post Step Therapy Prior Authorization ***Ref # 676-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.

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 BCise

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

Limitations of Use

- Bydureon/Bydureon BCise are 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.
- Bydureon/Bydureon BCise are not a substitute for insulin. Bydureon/Bydureon BCise 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/Bydureon BCise with insulin has not been studied.
- Bydureon/Bydureon BCise are extended-release formulations of exenatide. Bydureon/Bydureon BCise should not be used with other products containing the active ingredient exenatide.
- Bydureon/Bydureon BCise have not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies 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.

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
- 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

Limitations of Use

- 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.

Rybelsus

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

Limitations of Use

- Rybelsus 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
- Rybelsus has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis
- Rybelsus 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 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. 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 patients 10 years and older 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

Limitations of Use

- 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
- 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

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.
- 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 > 300 mg/day.

Limitations 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 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 when treatment with both canagliflozin and metformin HCl is appropriate.

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). However, the effectiveness of Invokamet/Invokamet XR on reducing major cardiovascular events in adults with type 2 diabetes and cardiovascular disease has not been established.

Limitations of Use

Not recommended in patients with type 1 diabetes mellitus 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 XR

Synjardy and Synjardy XR are 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/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/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.

Limitations of Use

Qtern is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

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.

SGLT2 INHIBITOR / DPP-4 INHIBITOR / METFORMIN:

Qternmet XR

Qternmet XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended-release tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

Qternmet XR is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
Qternmet XR initiation is intended only for patients currently taking 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.

Limitations of Use

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

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 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, COMBINATIONS:
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 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**
  - The patient has demonstrated a reduction in A1c (hemoglobin A1c) since starting this therapy
    OR
  - The request is for Farxiga (dapagliflozin), Invokana (canagliflozin), Jardiance (empagliflozin), Ozempic (semaglutide), or Victoza (liraglutide) 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 SymlinPen (pramlintide acetate) **AND**
  - The patient has a diagnosis of diabetes mellitus AND has failed to achieve desired glucose control despite receiving optimal insulin therapy, including mealtime insulin

OR

- The patient has a diagnosis of type 2 diabetes mellitus **AND**
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to metformin

  OR
  - The patient requires combination therapy AND has an A1c (hemoglobin A1c) of 7.5 percent or greater

  OR
  - The request is for Farxiga (dapagliflozin), Invokana (canagliflozin), Jardiance (empagliflozin), Ozempic (semaglutide), or Victoza (liraglutide) 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

RATIONALE

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 GLP-1 (glucagon-like peptide-1) receptor agonists, SGLT2 (sodium-glucose cotransporter 2) Inhibitors, and Combinations, 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. Adlyxin (lixisenatide), Bydureon/Bydureon BCise (exenatide extended-release), Byetta (exenatide), Farxiga (dapagliflozin), Glyxambi (empagliflozin/linagliptin), Invokana (canagliflozin), Invokamet (canagliflozin/metformin), Invokamet XR (canagliflozin/metformin extended-release), Jardiance (empagliflozin), Ozempic (semaglutide), Qtern (dapagliflozin/saxagliptin), Qternmet XR (dapagliflozin/saxagliptin/metformin extended-release), Rybelsus (semaglutide), Segluromet (ertugliflozin /metformin), Steglatro (ertugliflozin), Steglujan (ertugliflozin/ sitagliptin), Synjardy (empagliflozin/metformin), Synjardy XR (empagliflozin/metformin extended-release), Tanzeum (albiglutide), Trijardy XR (empagliflozin/linagliptin/metformin extended-release) Trulicity (dulaglutide), Victoza (liraglutide), and Xigduo XR (dapagliflozin and metformin extended-release) are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Farxiga (dapagliflozin) is also indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors.

Invokana (canagliflozin) is also 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); and 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 > 300 mg/day. However, the effectiveness of canagliflozin combination products such as Invokamet and Invokamet XR for these indications has not been established.

Jardiance (empagliflozin) is also indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of empagliflozin combination products such as Glyxambi, Synjardy, and Synjardy XR on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Ozempic (semaglutide) is also indicated 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.

Victoza (liraglutide) is also indicated 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.

SymlinPen (pramlintide acetate) 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.

Soliqua (insulin glargine and lixisenatide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended starting doses are determined based on the following: patients naïve to basal insulin or GLP-1 receptor agonist; patients currently on a GLP-1 receptor agonist; patients currently on less than 30 units of basal insulin daily; patients currently on 30-60 units of basal insulin, with or without a GLP-1 receptor agonist.

Xultophy (insulin degludec and liraglutide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended starting doses are determined based on the following: patients naïve to basal insulin or GLP-1 receptor agonist; patients currently on basal insulin or a GLP-1 receptor agonist.

Clinical guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists and American College of Endocrinology for the management of hyperglycemia in type 2 diabetes indicate that metformin monotherapy should be started at diagnosis of type 2 diabetes unless there are contraindications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. In patients with contraindications or intolerance of metformin, initial therapy should be based on patient factors; consider a drug from another class. [27, 28]

The clinical guidelines also state that the A1c test is the major tool for assessing glycemic control and has strong predictive value for diabetes complications. Thus, A1c testing should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care.[27] The guidelines set goals for therapeutic effectiveness which must be evaluated frequently (e.g., every 3 months) until stable, using multiple criteria, including A1c. Less frequent monitoring is acceptable once targets are achieved. [27, 28]

If the A1c target is not achieved after approximately 3 months and patient does not have atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), consider a combination of metformin and one of the preferred six treatment options: sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors. For patients in whom ASCVD, Heart Failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated cardiovascular risk reduction, after consideration of drug-specific and patient factors.[27, 28]

In patients with an initial A1c of 7.5% or greater, or in patients who are unable to achieve their glycemic goals with monotherapy, combination therapy is recommended.[28] Add-on therapy clinical studies with dapagliflozin plus saxagliptin in patients on metformin (i.e., Qternmet XR) were conducted – in one study (24-week randomized, double-blind, active-controlled, parallel group study in patients with an HbA1c ≥7.5% and ≤10.0%) patients were on a stable dose of metformin HCl (≥1500 mg per day) for at least 8 weeks prior to being randomized to one of three double-blind treatment groups to receive 5 mg dapagliflozin and 5 mg saxagliptin added to metformin, 5 mg saxagliptin and placebo added to metformin, or 5 mg dapagliflozin and placebo added to metformin. At Week 24, concomitant addition of 5 mg dapagliflozin and 5 mg saxagliptin plus metformin resulted in statistically significant decreases in HbA1c, and a larger proportion of patients

achieving the therapeutic glycemic goal of HbA1c <7%, compared to dapagliflozin plus metformin or saxagliptin plus metformin.[12] An add-on therapy clinical study with empagliflozin and linagliptin in patients on metformin (i.e., Trijardy XR) was conducted - the double-blind, active-controlled study evaluated the efficacy and safety of empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg, compared to the individual components. Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized to one of 5 active-treatment arms of empagliflozin 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg empagliflozin as a fixed dose combination tablet. At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin.[31] Additionally, the combination of basal insulin with a GLP1 receptor agonist (i.e., Soliqua, Xultophy) may offer greater efficacy than the oral agents.[28] This combination also has potent glucose lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens.[27]

Invokana (canagliflozin), Jardiance (empagliflozin), Ozempic (semaglutide),and Victoza (liraglutide) will be approved for initial therapy and continuation of therapy for type 2 diabetes mellitus patients who have established cardiovascular disease per the following: The CANVAS and CANVAS-R trials compared the risk of Major Adverse Cardiovascular Event (MACE) between canagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to standard of care for these diseases.[7] The EMPA-REG OUTCOME study compared the risk of experiencing a MACE between empagliflozin and placebo. Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard of care for these diseases.[9] The SUSTAIN 6 trial compared the risk of Major Adverse Cardiovascular Event (MACE) between semaglutide and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and cardiovascular disease.[10] In the LEADER trial, patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to liraglutide 1.8 mg or placebo. During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure.[22] Farxiga (dapagliflozin) will be approved for initial therapy and continuation of therapy for type 2 diabetes mellitus patients who have established cardiovascular disease or multiple cardiovascular risk factors per the following: The DECLARE trial compared the effect of dapagliflozin 10mg relative to placebo on cardiovascular outcomes when added to current background therapy. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of the investigators, to ensure participants were treated according to the standard of care for these diseases.[5]

Invokana (canagliflozin) will also be approved for initial therapy and continuation of therapy for type 2 diabetes mellitus patients who have diabetes with established nephropathy per the following: The CREDENCE trial compared canagliflozin with placebo in patients with type 2 diabetes mellitus, an estimated glomerular filtration rate ≥ 30 to < 90 mL/min/1.73 m^2 and albuminuria (urine albumin/creatinine > 300 to ≤ 5000 mg/g) who were receiving standard of care including a maximum-tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients were randomized to receive canagliflozin 100 mg or placebo and treatment was continued until the initiation of dialysis or renal transplantation.[8] The use of other background therapy for glycemic management and control of cardiovascular risk factors was recommended in accordance with local guidelines.[30]

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