Oscar Clinical Guideline: Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & SGLT2 Antidiabetic Combinations (PG154, Ver. 5)

Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & Antidiabetic Combinations

- **Biguanide, Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations**
  - Trijardy XR (Empagliflozin; Linagliptin; Metformin)
- **Biguanide and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors Antidiabetic Combinations**
  - Dapagliflozin/Metformin (Xigduo XR)
  - Invokamet (Canagliflozin; Metformin)
  - Invokamet XR (Canagliflozin; Metformin)
  - Segluromet (Ertugliflozin; Metformin)
  - Synjardy (Empagliflozin; Metformin)
  - Synjardy XR (Empagliflozin; Metformin)
- **Dipeptidyl Peptidase-4 (DDP-4) Inhibitor and Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations**
  - Glyxambi (Empagliflozin; Linagliptin)
  - Qtern (Dapagliflozin; Saxagliptin)
  - Steglujan (Ertugliflozin; Sitagliptin)
- **Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**
  - bexagliflozin (Brenzavvy)
  - dapagliflozin (Farxiga)
  - Inpefa (sotagliflozin)
  - Invokana (Canagliflozin)
  - Jardiance (Empagliflozin)
  - Steglatro (Ertugliflozin)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Sodium-glucose cotransporter-2 (SGLT2) inhibitors and their combination products represent an essential category of antidiabetic agents that reduce high blood sugar levels by decreasing renal glucose reabsorption and increasing urinary glucose excretion. They are employed to manage diabetes, a chronic medical condition characterized by high blood sugar levels resulting from inadequate insulin production by the pancreas, or the body's ineffective response to insulin.

Diabetes management often necessitates a combination of diet, exercise, and weight loss. Although Metformin is typically the initial treatment choice, certain patients may require the addition or substitution of an SGLT2 inhibitor or an incretin mimetic such as a glucagon-like peptide-1 (GLP-1) receptor agonist. The choice of a second antihyperglycemic drug generally depends on the presence of comorbid conditions such as ASCVD, heart failure (HF), CKD, and obesity.

Recent clinical trials have demonstrated that SGLT2 inhibitors offer significant cardiovascular and renal benefits beyond glycemic control. Key findings include:

- Cardiovascular benefits - Farxiga (dapagliflozin), Invokana (canagliflozin), and Jardiance (empagliflozin) have been shown to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established atherosclerotic cardiovascular disease (ASCVD). These benefits encompass reductions in cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
- Heart Failure management - Farxiga (dapagliflozin), Jardiance (empagliflozin), and Inpefa (sotagliflozin) have demonstrated efficacy in reducing hospitalizations for heart failure and

improving heart failure symptoms in patients with T2DM and heart failure (NYHA Class II-IV), even in those without diabetes.

- Renal protection - Farxiga (dapagliflozin), Invokana (canagliflozin), and Inpefa (sotagliflozin) have shown benefits in reducing the risk of end-stage kidney disease (ESKD), significant declines in estimated glomerular filtration rate (eGFR), and renal or cardiovascular death in patients with CKD at risk of progression.

NOTE:

1. The Plan requires that members either be unable to use, or have tried and failed preferred medication(s) first. Requests for non-formulary medications are subject to Non-Formulary Products Criteria (PG069).
2. Coverage for prescription medications intended for obesity treatment, weight loss, weight reduction, or dietary control is determined by each member's specific benefit policy. Please refer to the member's benefit plan document for information on benefit eligibility and terms of coverage. In cases where the plan includes coverage for drugs prescribed for obesity treatment or weight management, the Oscar Clinical Guideline: Weight Loss Agents (PG070) may also apply.

Table 1: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & Antidiabetic Combinations

Classification	Drug[#]	FDA-Approved Indications
Biguanide, Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations	Trijardy XR (Empagliflozin; Linagliptin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Invokamet (Canagliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Invokamet XR (Canagliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Biguanide and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors Antidiabetic Combinations	Segluromet (Ertugliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Synjardy (Empagliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Synjardy XR (Empagliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Xigduo XR (Dapagliflozin; Metformin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Dipeptidyl Peptidase-4 (DDP-4) Inhibitor and Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations	Glyxambi (Empagliflozin; Linagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Qtern (Dapagliflozin; Saxagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Steglujan (Ertugliflozin; Sitagliptin)	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.
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors	Brenzavvy (bexagliflozin)	● As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Farxiga (Dapagliflozin)	● 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 visit 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.
	Inpefa (sotagliflozin)	to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

		• heart failure or • type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors
	Invokana (Canagliflozin)	• 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.
	Jardiance (Empagliflozin)	1. to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. 2. 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. 3. to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. 4. as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Steglatro (Ertugliflozin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

[#] *include both brand and generic and all dosage forms and strengths unless otherwise stated*

Definitions

"**Insulin**" is a hormone produced by the beta cells in the pancreas. It facilitates the entry of glucose into cells for energy production. Insufficient insulin leads to a high blood glucose level, a condition known as diabetes. Oral and injectable medications can help increase insulin production, enhance the body's sensitivity to insulin, and decrease blood sugar levels.

"**Type 1 Diabetes**" is an autoimmune condition where the pancreas's beta cells are unable to produce sufficient insulin, leading to elevated blood glucose levels. Patients with Type 1 diabetes often require daily insulin injections to regulate their blood glucose.

"**Type 2 Diabetes**" is a metabolic disorder characterized by insufficient insulin production or insulin resistance in the body cells. It is more common than Type 1 and often managed through lifestyle changes, non-insulin medications, and, if necessary, insulin injections.

"**Blood Glucose**" is the primary sugar found in the bloodstream, serving as the body's main energy source. Chronic high blood glucose levels can lead to complications from blood vessel damage.

"**Hemoglobin A1c (HbA1c)**" is a blood test that measures average blood glucose levels over the past 2 to 3 months. It is also referred to as the A1C or glycosylated hemoglobin test. Various factors, such as age, ethnicity, certain conditions, and pregnancy, can affect A1C results.

"**Hyperglycemia**" is the medical term for high blood glucose. It can occur due to inadequate fasting (fasting hyperglycemia) or post-meal (postprandial hyperglycemia).

"**Hypoglycemia**" is a condition characterized by abnormally low blood glucose, typically less than 70 mg/dL. Symptoms include hunger, nervousness, dizziness, confusion, and in severe cases, unconsciousness. Immediate treatment involves consuming carbohydrate-rich foods or using injectable glucagon for severe cases.

"**Cardiovascular Disease**" refers to a class of diseases involving the heart and blood vessels. It is a common complication in individuals with long-term Type 2 diabetes and is often a key consideration when selecting an appropriate diabetes medication.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & Antidiabetic Combinations** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

For Type 2 Diabetes Mellitus:

1. The medication is age-appropriate for the member as per the FDA-approved indications***; AND***
2. The member has a diagnosis of type 2 diabetes mellitus based on at least **ONE** of the following diagnostic criteria:
    a. A fasting glucose level of greater than 126 mg/dL (7.0 mmol/L)****; and/or***
    b. A 2-hour glucose tolerance test result of greater than 200 mg/dL (11.1 mmol/L)****; and/or***
    c. A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher****; and/or***

d. Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia (e.g., frequent urination, extreme thirst, and unexplained weight loss) or hyperglycemic crisis***; AND***

Important Notes: **The American Diabetes Association (ADA) "Standards of Care in Diabetes" recommends, in the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.*

- ➢ *If two different tests are above diagnostic thresholds, this confirms the diagnosis without need for further testing.*
- ➢ *If two different tests are used and results are discordant, the test with a result above the diagnostic cut point should be repeated.*
- ➢ *For the Random Plasma Glucose test, a confirmatory test is not required if accompanied by classic symptoms of hyperglycemia or hyperglycemic crisis.*

3. The member has **ONE** of the following:
   a. is unable to use, or has adequately tried and failed metformin at a minimum effective dose of 1500 milligrams daily for 90 days***; or***
   b. requires combination therapy **AND** has an A1c (hemoglobin A1c) of 7.5 percent or greater***; or***
   c. chronic kidney disease (CKD) at risk of progression, **AND BOTH of the following**
      i. The member has an estimated glomerular filtration rate (eGFR) greater than or equal to 20 mL/min/1.73 m² (or as specified in the prescribing information); ***and***
      ii. **t**he request is for **ONE** of the following:
         1. Farxiga (dapagliflozin)***; or***
         2. Inpefa (sotagliflozin)***; or***
         3. Jardiance (empagliflozin)***; or***
   d. diabetic nephropathy with albuminuria greater than 300 mg per day, **AND** the request is for Invokana (canagliflozin)***; or***
   e. established Atherosclerotic Cardiovascular Disease (ASCVD) (e.g., coronary artery disease, cerebrovascular disease, peripheral arterial disease), **AND** the request is for **ONE** of the following:
      i. Farxiga (dapagliflozin)***; or***
      ii. Inpefa (sotagliflozin)***; or***
      iii. Invokana (canagliflozin)***; or***
      iv. Jardiance (empagliflozin)***; or***

f. multiple cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking, obesity, family history of premature ASCVD), **AND** the request is for Farxiga (dapagliflozin) or Inpefa (sotagliflozin)***; or***

g. New York Heart Association (NYHA) Class II-IV heart failure and the request is for **ONE** of the following:

i. Farxiga (dapagliflozin)***; or***

ii. Inpefa (sotagliflozin)***; or***

iii. Jardiance (empagliflozin)**.**

For Chronic Kidney Disease:

1. The request is for **ONE** of the following:
   a. Farxiga (dapagliflozin)***; and***
   b. Inpefa (sotagliflozin)***; and***
   c. Jardiance (empagliflozin)***; AND***
2. The member has chronic kidney disease at risk of progression**.**

For Heart Failure:

1. The request is for **ONE** of the following:
   a. Farxiga (dapagliflozin)***; and***
   b. Jardiance (empagliflozin)***; and***
   c. Inpefa (sotagliflozin)***; AND***
2. The member has New York Heart Association (NYHA) Class II-IV heart failure.

If the above prior authorization criteria are met, the requested drug will be approved for 12-months.

Medical Necessity Criteria for Re-authorization

Re-authorization for 12-months will be granted if the member meets **BOTH** the following criteria:

1. The requested medication is FDA-approved, or supported by current clinical practice guidelines or compendia for the member's specific diagnosis/indication***; AND***
2. The member has been using the requested medication and demonstrates an ongoing clinical benefit or need for continued therapy, as evidenced by **ONE** of the following:
   a. For Type 2 Diabetes Mellitus (T2DM):
      i. A reduction in Hemoglobin A1c (HbA1c) since initiation of therapy, documented within the past 6 months***; or***

ii. Maintenance of target HbA1c levels (e.g., HbA1c less than 7% or as determined by the treating provider based on member-specific goals)***; or***
iii. Improvement in fasting plasma glucose levels since initiation of therapy***; or***
iv. The member has established ASCVD (e.g., coronary artery disease, cerebrovascular disease, peripheral arterial disease)***; or***
v. The member has multiple cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking, obesity, family history of premature ASCVD)***; or***
vi. The member has diabetic nephropathy with significant albuminuria***; or***

b. The member has CKD with an estimated glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2 (or as specified in the prescribing information)***; or***
c. For Heart Failure (HF):
    i. Improvement or stabilization in heart failure symptoms (e.g., reduction in dyspnea, fatigue, edema)***; or***
    ii. Reduction in hospitalizations related to heart failure***; or***
    iii. Maintenance or improvement in New York Heart Association (NYHA) functional class.

NOTE: Providers should submit relevant clinical documentation supporting the member's continued benefit from the medication. This may include recent lab results, progress notes, or hospital discharge summaries. If the member's clinical status has changed (e.g., development of heart failure or CKD), and the medication is now prescribed for a new indication, the re-authorization request should reflect the current indication and meet the respective criteria outlined in the Initial Authorization *section.*

Experimental or Investigational / Not Medically Necessary

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & Antidiabetic Combinations for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

Appendix

Metformin in Type 2 Diabetes

[1]The recommendation for a minimum effective dose of 1500 milligrams daily of metformin is derived from clinical findings which show that this dosage effectively regulates both fasting blood glucose and glycosylated hemoglobin levels - crucial markers of long-term glucose control.

Metformin functions by decreasing glucose production in the liver and enhancing insulin sensitivity in both the liver and peripheral tissues. This enhancement in turn improves the uptake and usage of glucose. The efficacy of metformin is dose-dependent, with the most clinically meaningful responses usually not seen at doses below 1500 milligrams per day.

The strategy of starting metformin treatment at a lower dose and gradually stepping up the dose over time (typically over a period of weeks) is useful in reducing the occurrence and intensity of gastrointestinal side effects. These side effects are the most common adverse reactions linked with metformin therapy and can include symptoms such as nausea, vomiting, diarrhea, abdominal cramping, and bloating. Commencing therapy at a lower dose (for instance, 500 mg twice daily or 850 mg once daily) and progressively increasing the dosage over time allows patients to better tolerate metformin. This results in improved medication adherence and ultimately, superior glycemic control.

- For patients who need further glycemic control beyond what can be achieved with a total daily dose of 2000 mg, the dosage of metformin can be boosted up to a maximum of 2550 mg per day, given in divided doses. This upper limit is based on clinical trials that show doses above this level do not provide an additional glycemic control benefit but may increase the risk of adverse effects.
- For pediatric patients, the same principle of beginning at a lower dose and incrementally increasing applies, with a maximum limit of 2000 mg per day given in divided doses.

Table 2: Metformin in Diabetes Treatment

Clinical Consideration	Recommendation
Understanding Metformin	Metformin is frequently used due to its efficacy, cost-effectiveness, and cardiovascular benefits. However, GI adverse effects are common and could limit its use.
Managing Patient Expectations	Inform patients that side effects are often temporary and encourage patience during the dosage adjustment period.
Choosing Metformin Type	Extended-release (ER) versions are generally preferred due to fewer daily doses and reduced discontinuation rates. However, consider cost and insurance coverage.
Initiating Metformin	Start at a low dose (500 mg for ER/IR or 250 mg for those with GI intolerance history). Consider using liquid formulations or single-ingredient products for easier titration.

Dosage Increase	Gradually up titrate dosage every one to two weeks. Decrease back to the last tolerated dose if GI symptoms occur, and then try to increase more slowly.
Dosage Titration (Adults)	Dosage may be increased by 500 mg at weekly intervals until desired response or a maximum dosage is reached (2.55 g daily for immediate-release, 2.5 g for certain extended-release tablets, and 2 g for others).
Dosage Titration (Children 10–16 years)	Dosage may be increased by 500 mg at weekly intervals until desired response or a maximum dosage of 2 g daily in 2 divided doses is reached.
Maximizing Tolerance	Advice patients to take metformin during or immediately after meals. Consider dividing doses if tolerability is an issue.
Addressing Complaints	Manage common complaints such as diarrhea and nausea by temporary dose reduction. If odor of the drug is a problem, consider switching brands or generics.
GI Tolerance Issues	If GI symptoms persist, consider using 5-HT3-antagonists like ondansetron or treating underlying Helicobacter pylori infection.
Insufficient Dose Tolerance	Even lower doses can improve glucose control. Consider combining metformin with another agent if necessary.
Interrupted Therapy	If therapy is interrupted, consider a full titration when restarting. Lower the dose and increase slowly if adverse effects occur upon restarting.

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