Oscar Clinical Guideline: Antidiabetic Agents - Glucagon-like Peptide-1 (GLP-1) Receptor Agonists (PG152, Ver. 6)

Antidiabetic Agents - Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

- Dual Glucose-dependent Insulinotropic Polypeptide (GIP) and GLP-1 Receptor Agonists
  - Mounjaro (Tirzepatide)
- Glucagon-like Peptide-1 (GLP-1) Receptor Agonists
  - Bydureon BCise (Exenatide)
  - Byetta (Exenatide)
  - Liraglutide (Victoza)
  - Ozempic (Semaglutide)
  - Rybelsus (Semaglutide)
  - Trulicity (Dulaglutide)

Summary

Incretin mimetics, also known as glucagon-like peptide-1 (GLP-1) receptor agonists, are an important class of antidiabetic agents that potentiate glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety. They are used to manage diabetes, a long-term medical condition characterized by high blood sugar levels due to the pancreas not producing enough insulin, or the body not responding effectively to insulin.

- Tirzepatide (Mounjaro) is a unique dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. Clinical trials, including the SURPASS series, have demonstrated that tirzepatide significantly reduces hemoglobin A1c (HbA1c) levels (up to 2.8%) and body weight (up to 14.8 kg) compared to placebo, semaglutide, insulin degludec, and insulin glargine. Cardiovascular outcome studies are ongoing to assess its impact on major adverse cardiovascular events (MACE). A new single-dose vial formulation of tirzepatide is now available, offering additional administration options.
- Other notable GLP-1 receptor agonists include:
    - Exenatide extended-release (Bydureon BCise)
    - Exenatide immediate-release (Byetta)
    - Semaglutide injection (Ozempic)
    - Semaglutide oral (Rybelsus)
    - Dulaglutide (Trulicity)
    - Liraglutide (Victoza)

Several of these medications, particularly dulaglutide, liraglutide, and injectable semaglutide, have demonstrated cardiovascular benefits. They have been shown to reduce the risk of MACE in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors, aligning with the 2025 American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the 2022 American Association of Clinical Endocrinology (AACE) guidelines.

Ozempic (semaglutide) demonstrated reno-protective effects in adults with type 2 diabetes mellitus and chronic kidney disease, aligning with the 2025 American Diabetes Association (ADA) Standards of Medical Care in Diabetes.

Noteworthy updates include a safety warning for Ozempic (semaglutide) regarding increased reports of ileus, a potentially life-threatening intestinal blockage. Clinicians should monitor patients for signs of gastrointestinal obstruction and manage accordingly. Additionally, the 2025 ADA Standards of Medical

Care in Diabetes note concurrent use of dipeptidyl peptidase-4 (DPP-4) inhibitors with a GLP-1 RA or a dual GIP and GLP-1 RA is not recommended due to lack of additional glucose lowering beyond that of a GLP-1 RA alone.

Management of T2DM typically involves lifestyle modifications such as diet, exercise, and weight loss. Pharmacologic therapy is often necessary to achieve glycemic control. Metformin is generally preferred for initial treatment; however, GLP-1 receptor agonists with proven cardiovascular benefits are recommended for patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk.

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 varies depending on a member's specific benefit policy. Please refer to the member's benefit plan document for information on benefit eligibility and terms of coverage. This clinical guideline specifically addresses the use of GLP-1 receptor agonists for type 2 diabetes mellitus. Other indications are managed under separate guidelines.
    a. For coverage criteria related to the use of GLP-1 receptor agonists for weight management, please refer to the Oscar Clinical Guideline: Weight Loss Agents (PG070).
    b. For coverage criteria related to Wegovy (semaglutide) for cardiovascular risk reduction in adults with established cardiovascular disease and obesity or overweight, please refer to the Oscar Clinical Guideline: Wegovy for Cardiovascular Risk Reduction (PG194).
    c. For coverage criteria related to Zepbound (tirzepatide) for the treatment of moderate-to-severe obstructive sleep apnea in adults with obesity, please refer to the Oscar Clinical Guideline: Zepbound (tirzepatide) for the Treatment of Obstructive Sleep Apnea (PG255).

Table 1: Glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics)

Classification	Drug[#]	FDA-Approved Indications
Dual Glucose-dependent Insulinotropic Polypeptide (GIP) and GLP-1 Receptor Agonists	Mounjaro (tirzepatide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1 2]
Incretin mimetics Antidiabetics	Bydureon BCise	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with

	(exenatide)	type 2 diabetes mellitus [1 2 4 5]
	Byetta (exenatide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1 2 5]
	Ozempic (semaglutide)	Diabetes mellitus, type 2, treatment: [1 2] ● 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. ● to reduce the risk of sustained eGFR decline, end-stage kidney disease and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease.
	Rybelsus (semaglutide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1 2]
	Trulicity (dulaglutide)	Diabetes mellitus, type 2, treatment: [1 2] ● As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus; ● risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.
	Victoza (liraglutide)	Diabetes mellitus, type 2, treatment: [1 6] ● As an adjunct to diet and exercise to improve glycemic control in children ≥10 years of age, adolescents, and adults with type 2 diabetes mellitus; ● risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

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

<u>Limitations of Use:</u>

[1] has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis

[2] is not indicated for use in patients with type 1 diabetes mellitus

[3] has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

[4] 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

[5] should not be used with other products containing the active ingredient exenatide.

[6] should not be coadministered with other liraglutide-containing products.

Definitions

"Dipeptidyl Peptidase-4 (DPP-4) Inhibitors" are a class of oral antidiabetic drugs used primarily in the management of type 2 diabetes mellitus. DPP-4 inhibitors work by blocking the action of the DPP-4 enzyme, which is responsible for the degradation of incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Examples include alogliptin (Nesina), saxagliptin (Onglyza), sitagliptin (Januvia), Tradjenta (linagliptin), and Zituvio (sitagliptin). Examples of DDP-4 combinations include Jentadueto (linagliptin/metformin), Jentadueto XR (linagliptin/metformin), alogliptin/metformin (Kazano), saxagliptin/metformin (Kombiglyze XR), sitagliptin/metformin (Janumet), sitagliptin/metformin (Janumet XR), Zituvimet (sitagliptin/metformin), Zituvimet XR (sitagliptin/metformin), alogliptin/pioglitazone (Oseni), Glyxambi (empagliflozin/linagliptin), Qtern (dapagliflozin/saxagliptin), and Steglujan (ertugliflozin/sitagliptin).

"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.

"Incretin Mimetics" are a class of medications that imitate the function of incretins, natural hormones in the body that help lower post-meal blood sugar levels. These medications, also known as glucagon-like peptide-1 (GLP-1) receptor agonists, slow digestion, prevent the liver from making too much glucose, and help the pancreas produce more insulin when needed.

"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.

Clinical Indications

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Type 2 Diabetes Mellitus

The Plan considers glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics) medically necessary when ALL the following criteria are met:

1. The medication is age-appropriate for the member as per the FDA-approved indications*; AND*
    - ➢ *For Bydureon BCise, Trulicity, and Victoza, the member must be 10 years of age or older.*
    - ➢ *For other glucagon-like peptide-1 (GLP-1) receptor agonists, the member must be 18 years of age or older.*
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 mg daily for at least 90 days*; or*
    b. requires combination therapy to achieve glycemic control AND has an HbA1c of 7.5 percent or greater*; or*
    c. has 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. Liraglutide (Victoza)*; or*
        ii. Ozempic (semaglutide)*; or*
        iii. Trulicity (dulaglutide)*; or*
    d. has presence of multiple cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking, obesity, family history of premature ASCVD), AND the request is for Trulicity (dulaglutide)*; or*
    e. has CKD with an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m^2 or greater AND the request is for ONE of the following:
        i. Liraglutide (Victoza)*; or*
        ii. Ozempic (semaglutide)*; or*
        iii. Trulicity (dulaglutide)*; and*
4. The member is not receiving a GLP-1 receptor agonist or dual GIP and GLP-1 receptor agonist in combination with a DPP-4 inhibitor or DPP-4 antidiabetic combination.

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

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Indication-Specific Criteria

Type 2 Diabetes Mellitus

The Plan considers glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics) medically necessary when ALL the following criteria are met:

1. The member meets ONE of the following:
    a. A reduction in Hemoglobin A1c (HbA1c) since initiation of therapy, documented within the past 6 months*; or*
    b. Maintenance of target HbA1c levels (e.g., HbA1c less than 7% or as determined by the treating provider based on member-specific goals)*; or*
    c. Improvement in fasting plasma glucose levels since initiation of therapy*; or*
    d. Presence of established ASCVD, multiple cardiovascular risk factors, or Chronic Kidney Disease (CKD) AND the requested GLP-1 receptor agonist is ONE of the following agents with proven benefits in these conditions:

i. Liraglutide (Victoza)*; or*
ii. Ozempic (semaglutide)*; or*
iii. Trulicity (dulaglutide)*; and*

2. The member is not receiving a GLP-1 receptor agonist or dual GIP and GLP-1 receptor agonist in combination with a DPP-4 inhibitor or DPP-4 antidiabetic combination.

<u>If the above reauthorization criteria are met, the requested drug will be approved for 12-months.</u>

Experimental or Investigational / Not Medically Necessary

Glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

NOTE - This clinical guideline specifically addresses the use of GLP-1 receptor agonists for type 2 diabetes mellitus. For other indications, such as weight management and cardiovascular risk reduction, please refer to the respective clinical guidelines:

- *Weight Loss Agents (PG070), for coverage criteria related to the use of GLP-1 receptor agonists for weight management.*
- *Wegovy for Cardiovascular Risk Reduction (PG194), for coverage criteria related to Wegovy (semaglutide) for cardiovascular risk reduction in adults with established cardiovascular disease and obesity or overweight.*

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Appendix A

Metformin in Type 2 Diabetes

*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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