Oscar Clinical Guideline: Antidiabetic Agents - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 Antidiabetic Combinations (PG155, Ver. 4)

Antidiabetic Agents - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 Antidiabetic Combinations[1]

- **Biguanide and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Antidiabetic Combinations**
  - 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)
- **Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Antidiabetics**
  - alogliptin (Nesina)
  - saxagliptin (Onglyza)
  - sitagliptin (Januvia)
  - Tradjenta (linagliptin)
  - Zituvio (sitagliptin)
- **Dipeptidyl Peptidase-4 (DDP-4) Inhibitor and Thiazolidinedione (Glitazone) Antidiabetic Combinations**
  - alogliptin/pioglitazone (Oseni)

[1]*DPP-4 and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations are part of Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & SGLT2 Antidiabetic Combinations (PG154). Please refer to Oscar Clinical Guideline PG154 for coverage criteria.*

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

Diabetes mellitus (commonly referred to as diabetes) is a chronic (long-term) medical condition characterized by high blood glucose (sugar). This may be because the pancreas (an organ in the belly) does not make enough insulin (a hormone), or because the body is not responding to insulin the way it should. Insulin helps glucose get into cells in the body, giving it energy. With diabetes, sugar builds up in the blood because the body stops responding to insulin, or because there is not enough of it. Diabetes is broadly grouped into two types:

- Type 1 diabetes - the pancreas makes no insulin, or a very small amount
- Type 2 diabetes - cells in the body do not respond to insulin the way it should; sometimes, the pancreas also does not make enough insulin

Diabetes is usually managed by eating healthy foods, getting plenty of exercise, and sometimes medicines. Medicines are used to either control blood sugar, or to lower the chance of problems that can happen in the future because of diabetes. These medications can be insulin itself, or medications that help the body make more insulin or help insulin do its job.

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). These hormones are secreted from the gut in response to meals and stimulate insulin secretion in a glucose-dependent manner. By inhibiting DPP-4, the levels of these active incretins increase, enhancing the secretion of insulin and suppressing glucagon release, thereby lowering blood glucose levels.

DPP-4 inhibitors are generally used as second-line therapy for type 2 diabetes when lifestyle modifications and metformin have failed to achieve glycemic control. They can be used as monotherapy or in combination with other antidiabetic drugs including metformin, sulfonylureas, thiazolidinediones, and insulin.

- The efficacy of DPP-4 inhibitors in reducing glycosylated hemoglobin (HbA1c) levels is modest, with a reduction of approximately 0.5 to 1.0 percent, but they are well tolerated and have a neutral effect on body weight.
- In terms of cardiovascular safety, large randomized trials have demonstrated that DPP-4 inhibitors do not increase the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes who have established cardiovascular disease or are at high 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 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: Antidiabetic Agents - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 Antidiabetic Combinations⇅

Classification	Drug#	FDA-Approved Indications
Biguanide and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Antidiabetic Combinations	Janumet (Metformin; Sitagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Janumet XR (Metformin; Sitagliptin)	
	Jentadueto (Linagliptin; Metformin)	
	Jentadueto XR (Linagliptin; Metformin)	
	Kazano (Alogliptin; Metformin)	

	Kombiglyze XR (Metformin; Saxagliptin)	
	Zituvimet (sitagliptin/metformin)	
	Zituvimet XR (sitagliptin/metformin)	
Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Antidiabetics	Januvia (Sitagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, as monotherapy or combination therapy.
	Nesina (Alogliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
	Onglyza (Saxagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as monotherapy or combination therapy.
	Tradjenta (Linagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes as monotherapy or in combination with other antidiabetic agents.
	Zituvio (sitagliptin)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, as monotherapy or combination therapy.
Dipeptidyl Peptidase-4 (DDP-4) Inhibitor and Thiazolidinedione (Glitazone) Antidiabetic Combinations	Oseni (Alogliptin; Pioglitazone)	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*

[⇅]*DPP-4 and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations are part of Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & SGLT2 Antidiabetic Combinations (PG154). Please refer to Oscar Clinical Guideline PG154 for coverage criteria.*

Definitions

"Insulin" is a hormone made by the beta cells of the pancreas. Insulin allows glucose to enter the cells in the body for use in energy production, and when it is inadequate, the sugar remains in the blood leading to diabetes. There are a variety of oral and parenteral medications that can increase insulin production, increase the body's sensitivity to existing insulin and reduce blood sugar. Insulin can also be injected or infused when lifestyle changes and non-insulin medications are inadequate.

"Type 1 Diabetes" is an autoimmune condition that occurs when the beta cells of the pancreas are unable to produce enough insulin and therefore blood glucose cannot enter cells to be used for energy. Type 1 diabetes is often referred to as "insulin-dependent" because these patients require insulin daily to maintain their blood glucose at acceptable levels.

"Type 2 Diabetes" is a condition that occurs when either the pancreas doesn't produce enough insulin or the body cells become resistant to insulin. Type 2 diabetes is much more common than Type 1, and is often treated with combinations of lifestyle changes and non-insulin medications, although insulin can be required later in the disease course. Many individuals with Type 2 Diabetes are "insulin-requiring".

"Blood Glucose" is the main sugar found in the blood and the body's main source of energy. It is also called glucose or blood sugar. The blood level of glucose is noted in milligrams per deciliter (mg/dL). When blood sugar is too high for long periods of time, complications can occur as a result of blood vessel damage.

"Hemoglobin A1c (HbA1c)" is a test that measures a person's average blood glucose level over the past 2 to 3 months. It is also known as "A1C" or "glycosylated hemoglobin". A1C should be measured at least twice annually for stable glycemic control and at least quarterly for unstable glycemic control. A1C test results may be affected by age, certain conditions, ethnicity, genetic traits, and pregnancy; the ADA recommends that treating providers review for discrepancies between A1c results and blood glucose results.

"Hyperglycemia" is excessive blood glucose. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours. Postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

"Hypoglycemia" is a condition that occurs when one's blood glucose is lower than normal, usually less than 70 mg/dL. Signs include hunger, nervousness, shakiness, perspiration, dizziness or lightheadedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. Hypoglycemia is

treated by consuming a carbohydrate-rich food such as a glucose tablet or juice. It may also be treated with an injection of glucagon if the person is unconscious or unable to swallow.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 Antidiabetic Combinations**[⇅] medically necessary when **ALL** the following criteria are met:

[⇅]DPP-4 and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations are part of Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & SGLT2 Antidiabetic Combinations (PG154). Please refer to Oscar Clinical Guideline PG154 for coverage criteria.

1. The medication is age-appropriate for the member as per the FDA-approved indication***; 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.

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

Medical Necessity Criteria for Re-authorization

Reauthorization for 12 months will be granted if the member has been using the requested **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 Antidiabetic Combinations**[ℕ] and demonstrates an ongoing clinical need for continued therapy, as evidenced by **ONE** of the following:

[ℕ]DPP-4 and Sodium Glucose Co-transporter 2 (SGLT2) Inhibitor Antidiabetic Combinations are part of Antidiabetic Agents - Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors & SGLT2 Antidiabetic Combinations (PG154). Please refer to Oscar Clinical Guideline PG154 for coverage criteria.

1. A reduction in Hemoglobin A1c (HbA1c) since initiation of therapy, documented within the past 6 months***; or***
2. Maintenance of target HbA1c levels (e.g., HbA1c less than 7% or as determined by the treating provider based on member-specific goals)***; or***
3. Improvement in fasting plasma glucose levels since initiation of therapy**.**

Experimental or Investigational / Not Medically Necessary

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors & DPP-4 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

[ℕ]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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