# Antidiabetic Agents - Soliqua, Xultophy

- Insulins and Analogs and Incretin Mimetic Combinations
  - Soliqua (Insulin Glargine; Lixisenatide)
  - Xultophy (Insulin Degludec; Liraglutide)

## 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

Soliqua (insulin glargine; lixisenatide) and Xultophy (insulin degludec; liraglutide) are both fixed combination antidiabetic therapies used to manage type 2 diabetes, a chronic medical condition characterized by high blood sugar levels due to insufficient production of insulin by the pancreas, or the body not responding effectively to insulin.

Soliqua (insulin glargine; lixisenatide) is a combination of insulin glargine and lixisenatide, while Xultophy (insulin degludec; liraglutide) combines insulin degludec and liraglutide. Insulin glargine and insulin degludec are both long-acting insulin analogs (i.e., basal insulin), whereas lixisenatide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists. The latter class of drugs enhance glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety, thus assisting in the management of blood sugar levels.

Clinical trials have demonstrated the efficacy of both Soliqua (insulin glargine; lixisenatide) and Xultophy (insulin degludec; liraglutide). For instance, trials with insulin degludec/liraglutide (Xultophy) have shown that it is more effective than either drug alone in improving glycemic control, as determined by reductions in HbA1c, in those with type 2 diabetes mellitus. In several studies, the fixed combination substantially improved glycemic control and achieved superior outcomes in HbA1c reduction compared to placebo or individual components. However, it should be noted that the use of this combination is not indicated for the treatment of diabetic ketoacidosis,type 1 diabetes mellitus, or to be used in combination with another GLP-1 receptor agonist or prandial insulin.

Similarly, insulin glargine/lixisenatide (Soliqua) has been found to be more effective than either of its components alone in controlling blood sugar levels in type 2 diabetes patients. Clinical trials have shown a significantly greater reduction in HbA1c levels with the use of Soliqua (insulin glargine; lixisenatide) compared to insulin glargine alone. Interestingly, while insulin therapy is often associated with weight gain, Soliqua (insulin glargine; lixisenatide) therapy has been associated with weight loss, likely due to the GLP-1 agonist component.

Management of diabetes typically involves a combination of diet, exercise, and medication. When initial treatment with antihyperglycemic drugs like metformin is insufficient, adding or substituting with an Sodium-glucose cotransporter 2 (SGLT2) inhibitor or a GLP-1 receptor agonist (GLP-1 RA) may be considered. In cases where these options prove inadequate, fixed-combination therapies like Soliqua (insulin glargine; lixisenatide) and Xultophy (insulin degludec; liraglutide) may offer an effective alternative. These treatments offer the benefits of multiple antidiabetic agents, providing a more potent effect on blood glucose control.  Of note, the 2026 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 glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA is not recommended due to lack of additional glucose lowering beyond that of a GLP-1-based therapy alone.

Soliqua (insulin glargine; lixisenatide) is available as a 100/33 (100 units of insulin glargine to 33 mcg of lixisenatide per ml) prefilled 3 ml pen, which delivers 15 to 60 units of insulin glargine per injection. In those naive to insulin (or receiving less than 30 units of basal insulin daily) or GLP-1 RA, it is recommended to begin dosing at 15 units insulin glargine/5 mcg lixisenatide once daily, and increase in increments of 2 units (0.66 mcg lixisenatide) to 4 units (1.32 mcg lixisenatide) of insulin every week to achieve the individual's goal fasting glucose. In those already receiving, or inadequately controlled on,

30-60 units of basal insulin daily, regardless of prior experience with a GLP-1 RA, the starting dose is 30 units of insulin glargine/10 mcg lixisenatide; titrating as above. The maximum daily recommended dose is 60 units of insulin glargine and 20 mcg of lixisenatide.

Xultophy (insulin degludec; liraglutide) is available as a 100/3.6 (100 units of insulin degludec to 3.6 mg of liraglutide) prefilled 3 ml pen. In those naive to insulin or GLP-1 RA, it is recommended to begin dosing at 10 units insulin degludec/0.36 mg liraglutide once daily, and increase in increments of 2 units (0.072 mg liraglutide) of insulin once or twice weekly to achieve the individual's goal fasting glucose. In those already converting from basal insulin or a GLP-1 RA the beginning dose is 16 units insulin degludec/0.58 mg liraglutide once daily; titrating as above. The maximum daily recommended dose is 50 units of insulin degludec and 1.8 mg of liraglutide. Dose increases are always based on the insulin component of these combined prefilled pen products.

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 - Insulins and Analogs and Incretin Mimetic Combinations

| Classification | Drug[#] | FDA-Approved Indications |
|---|---|---|
| Insulins and Analogs and Incretin Mimetic Combinations | Soliqua (Insulin Glargine; Lixisenatide) | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1-3] |
| | Xultophy (Insulin Degludec; Liraglutide) | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1-3] |

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

*Limitations of Use:*

[1] Coadministration with any other product containing a GLP-1 receptor agonist is not recommended
[2] Not recommended for the treatment of diabetic ketoacidosis.
[3] Has not been studied in combination with prandial insulin.

## Definitions

"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.

"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).

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA" is a class of injectable antidiabetic drugs used primarily in the management of type 2 diabetes mellitus. Dual GIP/GLP-1 RAs work mimicking incretin in the body - benefits include but are not limited to: improving the feeling of satiety (e.g., fullness), regulation of appetite, delaying gastric emptying, improved insulin secretion from the pancreas (lowering blood glucose) and reduction of glucagon release (which increased blood sugar). There is only one dual GIP/GLP-1 RA on the market: tirzepatide (Mounjaro, Zepound).

"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.

"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.

"[s]" indicates state mandates may apply.

"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.

## Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Type-2 Diabetes Mellitus

The Plan considers Insulins and Analogs and Incretin Mimetic Combinations 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*
    a. The member has a diagnosis of type 2 diabetes mellitus; *AND*
2. The member has ONE (1) of the following:[s]
    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; *AND*
3. The requested medication will not be used concomitantly with another GLP-1 receptor agonist, dual GIP and GLP-1 receptor agonist, DPP-4 inhibitor, or DPP-4 antidiabetic combination.

If the above prior authorization criteria are met, the requested drug will be approved for up to 24-months.[s]

*Continued Care*

## Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Indication-Specific Criteria

Type-2 Diabetes Mellitus

The Plan considers Insulins and Analogs and Incretin Mimetic Combinations medically necessary when ALL the following criteria are met:

1. The member meets ONE (1) of the following:
    a. A reduction in Hemoglobin A1c (HbA1c) since initiation of therapy, documented within the past 6 months*; or*
    b. Attainment 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*; AND*
2. The requested medication will not be used concomitantly with another GLP-1 receptor agonist, dual GIP and GLP-1 receptor agonist, DPP-4 inhibitor, or DPP-4 antidiabetic combination.

If the above reauthorization criteria are met, the requested product will be authorized for up to 24 months[s]

## Experimental or Investigational / Not Medically Necessary[s]

Insulins and Analogs and Incretin Mimetic 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

*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 (GI) 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 individuals to better tolerate metformin. This results in improved medication adherence and ultimately, superior glycemic control.

- For those 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 pediatrics, 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 individuals 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 coverage on the individual's plan. |
| 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 individuals 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. |

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|---|---|
| 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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