Antidiabetic Agents - Soliqua, Xultophy

Summary

Soliqua and Xultophy 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 is a combination of insulin glargine and lixisenatide, while Xultophy combines insulin degludec and liraglutide. Insulin glargine and insulin degludec are both long-acting insulin analogs, 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 and Xultophy. 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 patients 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 or type 1 diabetes mellitus.

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 compared to insulin glargine alone. Interestingly, while insulin therapy is often associated with weight gain, Soliqua therapy has been associated with weight loss.

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 SGLT2 inhibitor or a GLP-1 receptor agonist may be considered. In cases where these options prove inadequate, fixed-combination therapies like Soliqua and Xultophy may offer an effective alternative. These treatments offer the benefits of multiple antidiabetic agents, providing a more potent effect on blood glucose control.

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 Medical Necessity Criteria for Non-Formulary Products (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	Soliqua	Adjunct to diet and exercise to improve glycemic control in

Analogs and Incretin Mimetic Combinations	(Insulin Glargine; Lixisenatide)	adults with type 2 diabetes mellitus. [1 2 3 4 5]
	Xultophy (Insulin Degludec; Liraglutide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [3 5 6 7]

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

Limitations of Use:

[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 recommended for use in combination with any other product containing a GLP-1 receptor agonist

[3] is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

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

[5] has not been studied in combination with prandial insulin.

[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.

[7] is not recommended for use in combination with any other product containing liraglutide or another

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.

Medical Necessity Criteria for Authorization

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***
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***; and/or***
    b. A 2-hour glucose tolerance test result of greater than 200 mg/dL.***; and/or***
    c. Hemoglobin A1c ≥6.5%***; and/or***
    d. Symptoms of hyperglycemia plus a random plasma glucose ≥200 mg/dL***; AND***
    NOTE: Abnormal results must be confirmed on a second occasion unless they are unequivocal.
3. The member has **ONE** of the following:
    a. is unable to use, or has adequately tried and failed metformin at a minimum 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. has been receiving the requested drug for at least 3 months, AND has demonstrated a reduction in A1c (hemoglobin A1c) since starting this therapy***.***

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

Experimental or Investigational / Not Medically Necessary

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 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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