About

70%

of adults with type 2 diabetes on basal insulin are

NOT AT A1C GOAL[1,a,b]

WHY IS THAT?

Sometimes basal insulin is not enough, even after increasing their doses[2,3]

With little or no effect on glycemic control, high insulin doses can increase the likelihood for[2,c]:

Increased rates of hypoglycemia

Additional weight gain

Are your patients experiencing

DIMINISHING A1C RETURNS

on basal insulin?

[a]2 years after initiation of basal insulin.
[b]Based on a retrospective medical records review of Humedica's electronic records database, including 14,457 patients with type 2 diabetes.
[c]Based on a database of 63 insulin glargine U-100 clinical trials between 1997 and 2007, of which 15 studies met inclusion criteria (n=2837).

Indications and Limitations of Use

Xultophy® 100/3.6 (insulin degludec and liraglutide injection) 100 units/mL and 3.6 mg/mL is a combination of insulin degludec and liraglutide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Xultophy® 100/3.6 is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Xultophy® 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist (GLP-1 RA).
- Xultophy® 100/3.6 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Xultophy® 100/3.6 has not been studied in combination with prandial insulin.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

- **Liraglutide, one of the components of Xultophy® 100/3.6, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Xultophy® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.**
- **Xultophy® 100/3.6 is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Xultophy® 100/3.6 and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Xultophy® 100/3.6.**

CONTRAINDICATIONS

- Xultophy® 100/3.6 is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to Xultophy® 100/3.6, either of the active substances, or any of its excipients. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide, one of the components of Xultophy® 100/3.6.

WARNINGS AND PRECAUTIONS

- **Risk of Thyroid C-cell Tumors:** If serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging, the patient should be further evaluated.

Please see additional Important Safety Information on the following pages.
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novo nordisk®

Xultophy® 100/3.6
insulin degludec & liraglutide injection
100 units/mL & 3.6 mg/mL

For patients uncontrolled on basal insulin

CHANGING TO A BASAL-BOLUS REGIMEN MAY BE THE NEXT STEP[3]

However, intensifying to basal-bolus therapy may increase[4,5]:

Risk of hypoglycemia

Weight gain

Regimen complexity

Is there an

EQUALLY EFFECTIVE APPROACH

to achieving glycemic control?

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide postmarketing. Observe patients carefully for signs and symptoms of pancreatitis (persistent severe abdominal pain, sometimes radiating to the back with or without vomiting). If pancreatitis is suspected, discontinue Xultophy® 100/3.6 promptly and if pancreatitis is confirmed, do not restart. Liraglutide, one of the components of Xultophy® 100/3.6, has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at a higher risk for development of pancreatitis on liraglutide.
- **Never Share a Xultophy® 100/3.6 Pen Between Patients,** even if the needle is changed. Sharing of the pen poses a risk for transmission of blood-borne pathogens.
- **Hyper- or Hypoglycemia with Changes in Xultophy® 100/3.6 Regimen:** Monitor blood glucose in all patients. Changes in Xultophy® 100/3.6 regimen may affect glycemic control. Changes should be made cautiously and under medical supervision. Adjustments in concomitant oral anti-diabetic treatment may be needed.
- **Overdose Due to Medication Errors:** Instruct patients to check the label before each injection since accidental mix-ups with insulin containing products can occur. Do not administer more than 50 units of Xultophy® 100/3.6 daily. Do not exceed the 1.8 mg maximum recommended dose of liraglutide or use with other GLP-1 RAs.
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin-containing products, including Xultophy® 100/3.6, and may be life-threatening. Increase monitoring with changes to: dose, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with hypoglycemia unawareness or renal or hepatic impairment.
- **Acute Kidney Injury:** Acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis, have been reported postmarketing for liraglutide, usually in association with nausea, vomiting, diarrhea, or dehydration. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.
- **Hypersensitivity and Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur. If a hypersensitivity reaction occurs, discontinue and treat per standard of care. Anaphylaxis and angioedema have been reported with other GLP-1 RAs. Use caution in a patient with a history of anaphylaxis or angioedema with other GLP-1 RAs because it is unknown whether such patients will be predisposed to these reactions with Xultophy® 100/3.6.
- **Acute Gallbladder Disease:** In a cardiovascular outcomes trial (LEADER trial) 3.1% of patients treated with liraglutide, one of the components of Xultophy® 100/3.6, versus 1.9% of placebo treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
- **Hypokalemia:** All insulin containing products, including Xultophy® 100/3.6 can lead to life-threatening hypokalemia, which may then cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
- **Fluid Retention and Congestive Heart Failure:** Patients using insulin containing products, including Xultophy® 100/3.6, with thiazolidinediones (TZDs) should be observed for signs and symptoms of heart failure. If heart failure develops, dosage reduction or discontinuation of the TZD must be considered.

ADVERSE REACTIONS

- The most common adverse reactions, reported in ≥5% of patients treated with Xultophy® 100/3.6 are nasopharyngitis, headache, nausea, diarrhea, increased lipase and upper respiratory tract infection.

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Xultophy® 100/3.6

insulin degludec & liraglutide injection

100 units/mL & 3.6 mg/mL

What could

XULTOPHY® 100/3.6 DO FOR YOUR ADULT PATIENTS WITH TYPE 2 DIABETES?[a]

Comparable A1C reductions vs basal-bolus therapy[4]

	Xultophy® 100/3.6 insulin degludec & liraglutide injection 100 units/mL & 3.6 mg/mL	insulin glargine U-100 + insulin aspart
Primary endpoint		
Mean A1C reduction[4,b]	**–1.5%**	–1.5%
Secondary endpoints		
Number of injections[4]	**1 injection**	up to 5 injections
Average insulin dose[4,c]	**40 units**	84 units
Severe or BG-confirmed symptomatic hypoglycemia[d] reported[4,e]	**1.1 events/PYE**	8.2 events/PYE
Weight change[4]	**–2.0 lb**	+5.7 lb

Xultophy® 100/3.6 is not indicated for weight loss. Weight gain can occur with insulin-containing products, including Xultophy® 100/3.6, and has been attributed to the anabolic effects of insulin.[6]

Study Design
DUAL VII: A 26-week, randomized, parallel, open-label, treat-to-target trial in adult patients with type 2 diabetes inadequately controlled (A1C 7%-10%) on insulin glargine U-100 (20-50 units daily) + metformin, comparing the efficacy and safety of Xultophy® 100/3.6 (n=252) with basal-bolus therapy (insulin glargine U-100 + insulin aspart [n=254]) both + metformin. The primary endpoint was change in A1C after 26 weeks of treatment. Secondary endpoints included change in laboratory-measured FPG, dose, change in body weight, percent of patients achieving A1C <7%, and episodes of hypoglycemia.[4]

BG=blood glucose; PYE=patient-year of exposure; FPG=fasting plasma glucose.

[a]For adults with type 2 diabetes inadequately controlled on basal insulin (<50 units) as an adjunct to diet and exercise.

[b]The difference in A1C effect observed in the trial may not necessarily reflect the effect that may be observed in the care setting where alternative insulin glargine and insulin aspart dosage can be used.

[c]The pretrial dose of insulin was 34 units in the Xultophy® 100/3.6 arm and 33 units in the basal-bolus arm. Patients could not increase their basal insulin or Xultophy® 100/3.6 doses by more than 4 units per week and they could not increase their insulin aspart doses by more than 2 units per injection per week. Average end-of-trial dose was 40 units of Xultophy® 100/3.6 vs 52 units basal + 32 units bolus.

[d]Severe or BG-confirmed symptomatic hypoglycemia: an event requiring assistance from another person to actively administer carbohydrate, glucagon, or other resuscitative actions or BG confirmed by a plasma glucose value (<56 mg/dL) with symptoms consistent with hypoglycemia.

[e]The clinical relevance of the difference in rates of severe hypoglycemia has not been established.

Important Safety Information (cont'd)

DRUG INTERACTIONS

- Certain drugs may affect glucose metabolism, requiring dose adjustment and close monitoring of blood glucose. The signs and symptoms of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine).
- Liraglutide-containing products, including Xultophy® 100/3.6, cause a delay of gastric emptying, and thereby have the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with liraglutide-containing products.

USE IN SPECIFIC POPULATIONS

- Xultophy® 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

References: 1. Curtis B, Lage MJ. Glycemic control among patients with type 2 diabetes who initiate basal insulin: a retrospective cohort study. *J Med Econ*. 2014;17(1):21-31. **2.** Reid T, Gao L, Gill J, et al. How much is too much? Outcomes in patients using high-dose insulin glargine. *Int J Clin Pract*. 2016;70(1):56-65. **3.** American Diabetes Association. Standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42(suppl 1):S90-S102. **4.** Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. *Diabetes Care*. 2018;41(5):1009-1016. **5.** Novolog [package insert]. Plainsboro, NJ: Novo Nordisk Inc; December 2018. **6.** Xultophy 100/3.6 [package insert]. Plainsboro, NJ: Novo Nordisk Inc; August 2019.

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