HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XULTOPHY 100/3.6 safely and effectively. See full prescribing information for XULTOPHY 100/3.6.

XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection), for subcutaneous use
Initial U.S. Approval: 2016

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Liraglutide, one of the components of XULTOPHY 100/3.6, causes 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 (5.1, 13.1).**
- **XULTOPHY 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).**

----------INDICATIONS AND USAGE ----------
XULTOPHY 100/3.6 is a combination of insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily) (1).

Limitations of Use (1):
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist.
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial insulin.

----------DOSAGE AND ADMINISTRATION----------
- Discontinue therapy with liraglutide or basal insulin prior to initiation of XULTOPHY 100/3.6 (2.1)
- Recommended starting dosage is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily (2.1)
- Administer once daily at same time each day with or without food (2.1)
- Maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide) (2.1)
- XULTOPHY 100/3.6 pen delivers doses from 10 to 50 units with each injection (2.1, 2.2); each XULTOPHY 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide (2.1).
- Use alternative antidiabetic products if patients require a XULTOPHY 100/3.6 daily dosage: (2.1)
  - Persistently below 16 units, or
  - Over 50 units.
- See Full Prescribing Information for titration recommendations (2.2)
- Inject subcutaneously in thigh, upper arm or abdomen (2.4)
- Do not administer intravenously, intramuscularly, or by an infusion pump (2.4)
- Do not dilute or mix with any other insulin products or solutions (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 units of insulin degludec per mL and 3.6 mg of liraglutide per mL in a 3 mL single-patient-use pen (3).

----------CONTRAINDICATIONS----------
- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Patients with a prior serious hypersensitivity reaction to XULTOPHY 100/3.6 or either of the active substances or any of its excipients (4).
- During episodes of hypoglycemia (4).

----------WARNINGS AND PRECAUTIONS----------
- Thyroid C-cell Tumors: See Boxed Warning (5.1).
- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis have been reported for liraglutide. Discontinue promptly if pancreatitis is suspected (5.2).
- Never share a XULTOPHY 100/3.6 pen between patients, even if the needle is changed (5.3).
- Hyper- or hypoglycemia with changes in XULTOPHY 100/3.6 regimen: Carry out under close medical supervision and increase frequency of blood glucose monitoring (5.4).
- Overdose due to medication errors: XULTOPHY 100/3.6 contains two drugs. Instruct patients to check label before injection since accidental mix-ups with insulin containing products can occur. Do not exceed the maximum dose or administer with other GLP-1 receptor agonists (5.5).
- Hypoglycemia: May be life-threatening. Increase monitoring with changes to: dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.6, 6.1).
- Acute Kidney Injury: Has been reported postmarketing for liraglutide, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion (5.7).
- 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 (5.8).
- Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.9).
- Fluid retention and congestive heart failure with use of thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.10).
- Macrovascular Outcomes: There have been no studies establishing conclusive evidence of macrovascular risk reduction with XULTOPHY 100/3.6 (5.11).

----------ADVERSE REACTIONS----------
The most common adverse reactions, reported in ≥5% of patients treated with XULTOPHY 100/3.6: nasopharyngitis, headache, nausea, diarrhea, increased lipase and upper respiratory tract infection (6).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Drugs that affect glucose metabolism: Adjustment of XULTOPHY 100/3.6 dosage may be needed; closely monitor blood glucose (7.1).
- Anti-Adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Hypoglycemia signs and symptoms may be reduced (7.1).
- Effects of delayed gastric emptying on oral medications: May impact absorption of concomitantly administered oral medications (7.2).

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy: XULTOPHY 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2016

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FULL PRESCRIBING 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 *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13)]*.**

- **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 *[see Contraindications (4), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

XULTOPHY 100/3.6 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 inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).

Limitations of Use:

- XULTOPHY 100/3.6 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 *[see Warnings and Precautions (5.1)]*.
- XULTOPHY 100/3.6 has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- XULTOPHY 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist *[see Warnings and Precautions (5.5)]*.
- 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

The following are important dosing information for XULTOPHY 100/3.6, a combination of insulin degludec and liraglutide:

- Discontinue therapy with liraglutide or basal insulin prior to initiation of XULTOPHY 100/3.6.
- The recommended starting dosage of XULTOPHY 100/3.6 is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily.
- Administer XULTOPHY 100/3.6 once-daily at the same time each day with or without food.
- The maximum daily dosage of XULTOPHY 100/3.6 is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide) *[see Warnings and Precautions (5.5)]*.
- The XULTOPHY 100/3.6 pen delivers doses from 10 to 50 units with each injection (see Table 1) *[see Dosage and Administration (2.2)]*
- Use alternative antidiabetic products if patients require a XULTOPHY 100/3.6 daily dosage:
  - Persistently below 16 units *[Dosage and Administration (2.2)]*, or
  - Over 50 units.

Table 1 presents the units of insulin degludec and the milligrams of liraglutide in each dosage of XULTOPHY 100/3.6.

Table 1: Units of Insulin Degludec and Milligrams of Liraglutide in Each Dosage of XULTOPHY 100/3.6

XULTOPHY 100/3.6 (dose counter display)*	insulin degludec component dose	liraglutide component dose	Comment
▪▪ —	---	---	Priming symbol
10	10 units	0.36 mg	Temporary dose for down titration
11	11 units	0.4 mg	Temporary dose for down titration
12	12 units	0.43 mg	Temporary dose for down titration
13	13 units	0.47 mg	Temporary dose for down titration
14	14 units	0.5 mg	Temporary dose for down titration
15	15 units	0.54 mg	Temporary dose for down titration
16	**16 units**	**0.58 mg**	**Recommended starting dosage**
17	17 units	0.61 mg	
18	18 units	0.65 mg	
19	19 units	0.68 mg	
20	20 units	0.72 mg	
21	21 units	0.76 mg	
22	22 units	0.79 mg	
23	23 units	0.83 mg	
24	24 units	0.86 mg	
25	25 units	0.9 mg	
26	26 units	0.94 mg	
27	27 units	0.97 mg	
28	28 units	1.01 mg	
29	29 units	1.04 mg	
30	30 units	1.08 mg	
31	31 units	1.12 mg	
32	32 units	1.15 mg	
33	33 units	1.19 mg	
34	34 units	1.22 mg	
35	35 units	1.26 mg	
36	36 units	1.3 mg	
37	37 units	1.33 mg	
38	38 units	1.37 mg	

39	39 units	1.4 mg	
40	40 units	1.44 mg	
41	41 units	1.48 mg	
42	42 units	1.51 mg	
43	43 units	1.55 mg	
44	44 units	1.58 mg	
45	45 units	1.62 mg	
46	46 units	1.66 mg	
47	47 units	1.69 mg	
48	48 units	1.73 mg	
49	49 units	1.76 mg	
50	**50 units**	**1.8 mg**	**Maximum daily dosage** ***[see Warnings and Precautions (5.5)]***

* The dose counter on the XULTOPHY 100/3.6 pen displays numbers for the even units and displays lines for the odd units.

2.2 Titration of XULTOPHY 100/3.6

- After starting with 16 units of XULTOPHY 100/3.6 (16 units of insulin degludec and 0.58 mg of liraglutide), titrate the dosage upwards or downwards by **two units** (see Table 2) every three to four days based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved. The dosage of XULTOPHY 100/3.6 is between 16 to 50 units (see Table 1).
- The XULTOPHY 100/3.6 dosage may be temporarily down titrated to below 16 units (i.e., 10 to 15 units). However, if patients require persistent dosages below 16 units of XULTOPHY 100/3.6, discontinue and use alternative therapy (see Table 1).
- To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Table 2: Recommended Titration of XULTOPHY 100/3.6 (Every Three to Four Days)[1]

Self-Monitored Fasting Plasma Glucose	**XULTOPHY 100/3.6 Dosage Adjustment**
Above target range	+ 2 units (2 units of insulin degludec and 0.072 mg of liraglutide)
Within target range	0 units
Below target range	- 2 units (2 units of insulin degludec and 0.072 mg of liraglutide)

[1] The recommended XULTOPHY 100/3.6 dosage is between 16 to 50 units (see Table 1)

2.3 Missed Doses

- Instruct patients who miss a dose of XULTOPHY 100/3.6 to resume the once-daily regimen as prescribed with the next scheduled dose. Do not administer an extra dose or increase the dose to make up for the missed dose.
- If more than three days have elapsed since the last XULTOPHY 100/3.6 dose, reinitiate XULTOPHY 100/3.6 at the starting dose (i.e., 16 units) to mitigate any gastrointestinal symptoms associated with reinitiation of treatment *[see Dosage and Administration (2.1, 2.2)]*.

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