WARNING: RISK OF THYROID C-CELL TUMORS
See Boxed Warning (5.1).

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).

**DOSAGE FORMS AND STRENGTHS**
Injection 100 units/mL of insulin degludec and 3.6 mg/mL of liraglutide available in:
- 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).
- **WARNINGS AND PRECAUTIONS**
- Thyroid C-cell Tumors: See Boxed Warning (5.1).
Xultophy® 100/3.6 (insulin degludec and liraglutide) injection

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.

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 tumors findings to humans [see Warnings and Precautions (5.5)].
- 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

- XULTOPHY® 100/3.6 is a combination of insulin degludec and liraglutide.
- Administer XULTOPHY® 100/3.6 by subcutaneous injection once-daily at the same time each day with or without food.
- The XULTOPHY® 100/3.6 pen delivers doses from 10 to 50 units with each injection. Table 1 presents the units of insulin degludec and the milligrams of liraglutide in each dosage of XULTOPHY® 100/3.6 [see Dosage and Administration (2.2)].
- The maximum dose of XULTOPHY® 100/3.6 is 50 units daily (50 units of insulin degludec and 1.8 mg of liraglutide) [see Warnings and Precautions (5.6)].

2.2 Recommended Starting Dose

- In patients naïve to basal insulin or a GLP-1 receptor agonist
  - The recommended starting dose of XULTOPHY® 100/3.6 is 10 units (10 units of insulin degludec and 0.36 mg of liraglutide) given subcutaneously once-daily (see Table 1).
- In patients currently on basal insulin or a GLP-1 receptor agonist
  - Discontinue therapy with basal insulin or GLP-1 receptor agonist prior to initiation of XULTOPHY® 100/3.6.
  - The recommended starting dose of XULTOPHY® 100/3.6 is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once-daily (see Table 1).

2.3 Titration of XULTOPHY® 100/3.6

- After starting the recommended starting dose of XULTOPHY® 100/3.6 [see Dosage and Administration (2.2)], titrate the dosage upwards or downwards by two units (see Table 2) once weekly or twice weekly (every three to four days), based on the patient’s metabolic control, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved.
- 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 1: Units of Insulin Degludec and Milligrams of Liraglutide in Each Dosage of XULTOPHY® 100/3.6

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6 (dose counter display)</th>
<th>Insulin degludec component dose</th>
<th>Liraglutide component dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10 units</td>
<td>0.36 mg</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11 units</td>
<td>0.4 mg</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12 units</td>
<td>0.43 mg</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>13 units</td>
<td>0.47 mg</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>14 units</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>15 units</td>
<td>0.54 mg</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>16 units</td>
<td>0.56 mg</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Recommended Titration of XULTOPHY® 100/3.6 (Once or Twice Weekly)

<table>
<thead>
<tr>
<th>Self-Monitored Fasting Plasma Glucose</th>
<th>XULTOPHY® 100/3.6 Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above target range</td>
<td>+2 units (2 units of insulin degludec and 0.012 mg of liraglutide)</td>
</tr>
<tr>
<td>Within target range</td>
<td>0 units (2 units of insulin degludec and 0.012 mg of liraglutide)</td>
</tr>
<tr>
<td>Below target range</td>
<td>-2 units (2 units of insulin degludec and 0.012 mg of liraglutide)</td>
</tr>
</tbody>
</table>

2.4 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 recommended starting dose to mitigate any gastrointestinal symptoms associated with reinitiation of treatment [see Dosage and Administration (2.1, 2.2, 2.3)].

2.5 Important Administration Instructions

- The XULTOPHY® 100/3.6 pen is for single-patient-use only [see Warnings and Precautions (5.3)].
- Train patients on proper use and injection technique before initiating XULTOPHY® 100/3.6.
- Always check the label on the XULTOPHY® 100/3.6 pen before administration [see Warnings and Precautions (5.5)].
- Inspect visually for particulate matter and discoloration prior to administration. Only use XULTOPHY® 100/3.6 if the solution appears clear and colorless.
- Inject XULTOPHY® 100/3.6 subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see Warnings and Precautions (5.4), Adverse Reactions (6.1, 6.3)].
- During changes to a patient’s insulin regimen, increase the frequency of blood glucose monitoring [see Warnings and Precautions (5.4)].
- Use XULTOPHY® 100/3.6 with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
- The XULTOPHY® 100/3.6 pen dials in one-unit increments.
- Do not administer XULTOPHY® 100/3.6 intravenously or in an insulin infusion pump.
- Do not dilute or mix XULTOPHY® 100/3.6 with any other insulin or solutions.
- Do not split the dose of XULTOPHY® 100/3.6.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL insulin degludec and 3.6 mg/mL liraglutide available as a clear, colorless solution in a 3 mL pre-filled, disposable, single-patient-use pen injector.

4 CONTRAINDICATIONS

XULTOPHY® 100/3.6 is contraindicated:

- In patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 ( MEN 2) [see Warnings and Precautions (5.1)].
- During episodes of hypoglycemia [see Warnings and Precautions (5.6)].
- In patients with hypersensitivity to insulin degludec, liraglutide, or any of the excipients in XULTOPHY® 100/3.6. Serious hypersensitivity reactions including anaphylactic reactions and anaphylactoid events have been reported with liraglutide, one of the components of XULTOPHY® 100/3.6 [see Warnings and Precautions (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 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 in laboratory animals. In humans, the relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined [see Warnings and Precautions (5.1) and Nonclinical Toxicology (15)].

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)).

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

Recommended starting dose for patients naïve to basal insulin or GLP-1 receptor agonist

Table 1 presents the units of insulin degludec and the milligrams of liraglutide in each dosage of XULTOPHY® 100/3.6 [see Dosage and Administration (2.2)].

Maximum daily dosage [see Warnings and Precautions (5.5)]
5.2 Pancreatitis
Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with lixilaglutide, one of the components of XULTOPHY 100/3.6. In glycemic control trials of lixilaglutide, there were 13 cases of pancreatitis among lixilaglutide-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with lixilaglutide were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a lixilaglutide-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholecystectomy or alcohol abuse. Following initiation of XULTOPHY 100/3.6, observe patients carefully for signs and symptoms of pancreatitis (including persistent, severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, XULTOPHY 100/3.6 should be promptly discontinued and appropriate management should be initiated. If pancreatitis is confirmed, restarting XULTOPHY 100/3.6 is not recommended.

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 higher risk for recurrent pancreatitis in XULTOPHY 100/3.6.

5.3 Never Share a XULTOPHY 100/3.6 Pen Between Patients
XULTOPHY 100/3.6 pen must never be shared between patients, even if the needle is changed. Sharing of the pen poses a risk for transmission of blood-borne pathogens.

5.4 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen
Changing insulin regimens (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [See Warnings and Precautions (5.6)] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in a decreased effect of insulin and a change in the injection site (to an unaffected area) has been reported to result in hyperglycemia [See Adverse Reactions (6.1, 6.3)]. Make any changes to a patient’s insulin regimen under close medical supervision with increased glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. Adjustments in concurrent oral anti-diabetic treatment may be needed. When initiating XULTOPHY 100/3.6, follow dosing recommendations [See Dosage and Administration (2.1, 2.2, 2.3)].

5.5 Overdose due to Medication Errors
XULTOPHY 100/3.6 contains two drugs: insulin degludec and liraglutide. Administration of more than 50 units of XULTOPHY 100/3.6 daily can result in overdose of the liraglutide component. Do not exceed the 1.8 mg maximum recommended dose of liraglutide or use with other glucagon-like peptide-1 receptor agonists. Accidental mix-ups between insulin products have been reported. To avoid medication errors between XULTOPHY 100/3.6 (an insulin containing product) and other insulin products, instruct patients to always check the label before each injection.

5.6 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin containing products, including XULTOPHY 100/3.6 [See Adverse Reactions (6.1)]. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration and ability to drive or operate machinery. If hypoglycemia is probable, the patient should be evaluated by a physician. Hypoglycemia may be less evident in patients with diabetes that are elderly, are debilitated, and are using sympathomimetic drugs (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcium or using thyroid ultrasound is of no certain value for early detection of MTC in patients treated with XULTOPHY 100/3.6. Such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcium elevation and for the detection of thyroid disease.

Significantly elevated serum calcium may indicate MTC and patients with MTC usually have calcium values >50 mg/L. If serum calcium is measured and found to be elevated, the patient should be further evaluated, including imaging, to rule out nodules noted on physical examination or neck imaging should also be further evaluated.

5.8 Hypersensitivities Reactions
The risk of hypersensitivity generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin [See Clinical Pharmacology (12.2)]. and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin containing products, the glucose lowering effect time course of XULTOPHY 100/3.6 may vary among different patients or at different times in the same patient and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to concomitant drugs [See Drug Interactions (7.1)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [See Use in Specific Populations (8.6, 8.7)].

5.9 Risk Mitigation Strategies for Hypoglycemia
Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.10 Hypoglycemia
Hypoglycemia can happen suddenly and symptoms may differ in each patient and change over time in the same patient. Symptomatic awareness of hypoglycemia may be less pronounced in patients with diabetes being treated with an insulin PPAR-gamma agonist compared to shorter acting insulins.

The long-acting effect of insulin degludec may delay recovery from hypoglycemia compared to shorter acting insulins.

5.11 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR Gamma Agonist
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists can cause dose related fluid retention and weight gain. Untreated insulin can cause hypoglycemia, including XULTOPHY 100/3.6. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated with insulin containing products, including XULTOPHY 100/3.6 and a PPAR-gamma agonist should be observed for signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be managed according to current standards of care and discontinuation or decrease of the PPAR-gamma agonist must be considered.

6. ADVERSE REACTIONS
The following serious adverse reactions are described below or elsewhere in the prescribing information.

Risk of Thyroid C-cell Tumors [See Warnings and Precautions (5.1)]
• Pancreatitis [See Warnings and Precautions (5.2)]
• Hypoglycemia [See Warnings and Precautions (5.6)]
• Acute Kidney Injury [See Warnings and Precautions (5.7)]
• Hypersensitivity Reactions [See Warnings and Precautions (5.8)]
• Acute Gallbladder Disease [See Warnings and Precautions (5.9)]
• Hypokalemia [See Warnings and Precautions (5.10)]

6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

XULTOPHY 100/3.6
The data in Table 3 reflect the exposure of 1881 patients to XULTOPHY 100/3.6 and a mean duration of exposure of 33 weeks in trials NCT01392573, NCT01618162, NCT02773368, NCT01676116, NCT01392573, NCT01952145 [See Clinical Trials (14.2 and 14.3)]. The mean was 57 years and 75% were male, 75% were White, 6% were Black or African American and 16% were Hispanic or Latino. The mean body mass index (BMI) was 31.8 kg/m². The mean duration of diabetes was 9 years and the mean HbA1c at baseline was 8.2%. A history of nephropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 25%, 12%, 7% and 6% respectively. The mean estimated glomerular filtration rate (eGFR) at baseline was 88.3 mL/min/1.73 m² and 6% of the patients had an eGFR less than 60 mL/min/1.73 m².

Table 3: Adverse Reactions Occurring in ≥5% of XULTOPHY 100/3.6-Treated Patients with Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N = 1881 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>9.6</td>
</tr>
<tr>
<td>Headache</td>
<td>9.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.5</td>
</tr>
<tr>
<td>Increased Lipase</td>
<td>6.7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Hypoglycemia
Hypoglycemia was the most commonly observed adverse reaction in patients treated with insulin and insulin containing products, including XULTOPHY 100/3.6 [See Warnings and Precautions (5.6)]. The number of reported hypoglycemia episodes depended on the definition of hypoglycemia used, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic factors leading to hypoglycemia. Untreated hypoglycemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypoglycemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).
**Table 4: Hypoglycemia Episodes Reported in XULTOPHY® 100/3.6-Treated Patients with T2DM**

<table>
<thead>
<tr>
<th>Patients naïve to basal insulin or GLP-1 receptor agonist</th>
<th>Patients currently on GLP-1 receptor agonist</th>
<th>Patients currently on basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>XULTOPHY® 100/3.6 NCT01335023</td>
<td>XULTOPHY® 100/3.6 NCT01616162</td>
<td>XULTOPHY® 100/3.6 NCT01952573</td>
</tr>
<tr>
<td>825</td>
<td>288</td>
<td>209</td>
</tr>
<tr>
<td>209</td>
<td>281</td>
<td>199</td>
</tr>
<tr>
<td>278</td>
<td>199</td>
<td>100/3.6 NCT01952145</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Subjects (N)</th>
<th>Hypoglycemia (%)</th>
<th>Hypoglycemia with a glucose level ≤54 mg/dL (%)</th>
<th>Hypoglycemia with a glucose level &gt;54 mg/dL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>825</td>
<td>0.7</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>288</td>
<td>0.7</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>209</td>
<td>0.3</td>
<td>14.4</td>
<td>27.1</td>
</tr>
<tr>
<td>281</td>
<td>0.3</td>
<td>22.1</td>
<td>21.8</td>
</tr>
<tr>
<td>199</td>
<td>0.5</td>
<td>0.0</td>
<td>24.8</td>
</tr>
</tbody>
</table>

**Hypoglycemia Reactions**

- Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasmy, hypotension, and shock have occurred with insulin, including XULTOPHY® 100/3.6 and may be life threatening (see Warnings and Precautions (5.8)).

**Gastrointestinal Adverse Reactions**

- Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gas, abdominal pain, flatulence, eructation, gastrooesophageal reflux disease, abdominal distension and generalized abdominal pain have been reported in patients treated with XULTOPHY® 100/3.6. Gastrointestinal adverse reactions may occur more frequently at the beginning of XULTOPHY® 100/3.6 therapy and diminish within a few days or weeks on continued treatment.

**Papillary thyroid carcinoma**

**VICTOZA® (liraglutide)**

In glycemic control trials of liraglutide, there were 7 reported cases of papillary thyroid carcinoma in patients treated with liraglutide and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

**Cholelithiasis and cholecystitis**

**VICTOZA® (liraglutide)**

In a cardiovascular outcomes trial (LEADER trial) see Clinical Studies (14.4), the incidence of cholelithiasis was 1.5% (9.3 cases per 1000 patient years of observation) in liraglutide- and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in liraglutide-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients. The majority of events required hospitalization or cholecystectomy.

**Initiation of insulin containing products and intensification of glucose control**

- Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

**Lipodystrophy**

- Long-term use of insulin containing products, including XULTOPHY® 100/3.6, can cause lipodystrophy at the site of repeated injections.

- Lipodystrophy includes lipoatrophy (thinning of adipose tissue) and lipohypertrophy (thickening of adipose tissue), and may affect absorption (see Dosage and Administration (2.5)).

**Peripheral Edema**

**XULTOPHY® 100/3.6** may cause sodium retention and edema, particularly if previously poor metabolic control is improved rapidly by intensified therapy.

**Weight Gain**

- Weight gain can occur with insulin containing products, including XULTOPHY® 100/3.6, and has been attributed to the anabolic effects of the insulin component. In Study A, after 26 weeks of treatment, patients converting to XULTOPHY® 100/3.6 from liraglutide had a mean increase in body weight of 2 kg.

**Injection Site reactions**

- As with any insulin and GLP-1 receptor agonist-containing products, patients taking XULTOPHY® 100/3.6 may experience injection site reactions including injection site hematoma, pain, homorrhage, erythema, nodules, swelling, discolouration, pruritis, warmth, and injection site mass. In the clinical program, the proportion of injection site reactions occurring in patients treated with XULTOPHY® 100/3.6 was 2.6%. These reactions were usually mild and transitory and they normally disappear during continued treatment.
into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

Liraglutide
- Medullary thyroid carcinoma
- Dehydration resulting from nausea, vomiting and diarrhea
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis
- Angioedema and anaphylactic reactions
- Allergic reactions: rash and pruritus
- Skin and subcutaneous tissue disorder: cutaneous amyloidosis
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death
- Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, cholecytitis, cholethiasis requiring cholecystectomy, hepatitis

7 DRUG INTERACTIONS

7.1 Medications That Can Affect Glucose Metabolism
A number of medications affect glucose metabolism and may require dose adjustment of XULTOPHY 100/3.6 and particularly close monitoring [see Dosage and Administration (2.2); Warnings and Precautions (5.6)].

Effect of XULTOPHY
Drugs That May Increase the Risk of Hypoglycemia

- Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, hexobarbital, meperidine, minoxidil, metoclopramide, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics

Intervention: Dosage reductions and increased frequency of glucose monitoring may be required when XULTOPHY 100/3.6 is co-administered with these drugs.

Drugs That May Decrease the Blood Glucose Lowering Effect of XULTOPHY 100/3.6

- Alcohol, beta-blockers, clonidine, and lithium salts.
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Intervention: Dosage increases and increased frequency of glucose monitoring may be required when XULTOPHY 100/3.6 is co-administered with these drugs.

Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of XULTOPHY 100/3.6

- Drugs: Alcohol, beta-blockers, clonidine, and lithium salts.

Intervention: Dosage adjustment and increased frequency of glucose monitoring may be required when XULTOPHY 100/3.6 is co-administered with these drugs.

Drugs That May Blunt Signs and Symptoms of Hypoglycemia

- Beta-blockers, clonidine, guanethidine, and reperistep

Intervention: Increased frequency of glucose monitoring may be required when XULTOPHY 100/3.6 is co-administered with these drugs.

7.2 Effects of Delayed Gastric Emptying on Oral Medications
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. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree [see Clinical Pharmacology (12.3)]. Nonetheless, caution should be exercised when oral medications are concomitantly administered with liraglutide containing products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on animal reproduction studies, there is a risk to the fetus from exposure to liraglutide during pregnancy. XULTOPHY 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no available data with XULTOPHY 100/3.6, insulin degludec or liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnant women [see Clinical Pharmacology (12.3)].

For insulin degludec, rats and rabbits were exposed in animal reproduction studies at 5 times (rat) and 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. No adverse outcomes were observed for pregnant animals and offspring [see Data].

For liraglutide, maximum reproductive study doses of ≥7 and has been reported to be as high as 20 to 25% in women with a periconceptional HbA1c >10. The estimated background risk for miscarriage for the indicated population is unknown.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypoglycemia and hyperglycemia occur more frequently during pregnancy in patients with pre-gestational diabetes. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes mellitus increases the fetal risk for major birth defects, stillbirth, macrosomia related morbidity.

Data

Animal Data

Insulin degludec
Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryo-fetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec was given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall the effects of insulin degludec were similar to those observed with human insulin.

Liraglutide
Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-3, 11-times the human exposure at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD [see Data].

In pregnant rats, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a periconceptional HbA1c >7 and has been reported to be as high as 20 to 25% in women with a periconceptional HbA1c >10. The estimated background risk for miscarriage for the indicated population is unknown.

8.2 Lactation

Risk Summary
There are no data on the presence of liraglutide or insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. In lactating rats, insulin degludec and liraglutide, the two components of XULTOPHY 100/3.6, were present in milk.

The developmental and health benefits of breastfeeding should be considered in any decision to discontinue breastfeeding and the use of the drug in a nursing mother.

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

Liraglutide
In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

Data

Insulin degludec
In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

Liraglutide
In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use
Safety and effectiveness of XULTOPHY 100/3.6 have not been established in pediatric patients.

8.5 Geriatric Use

For the total number of 1818 subjects in clinical studies of XULTOPHY 100/3.6, 375 (19.9%) were 65 years and over, and 52 (2.8%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals to the effects of XULTOPHY 100/3.6 cannot be ruled out.

Age had no clinically relevant effect on the pharmacokinetics of XULTOPHY 100/3.6 [see Clinical Pharmacology (12.3)].

In geriatric patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be more difficult to recognize in geriatric patients.

8.6 Renal Impairment

XULTOPHY 100/3.6

There is limited experience with XULTOPHY 100/3.6 in patients with mild and moderate kidney impairment and when used in these patients, additional glucose monitoring and XULTOPHY 100/3.6 dose adjustment may be required in some individuals. XULTOPHY 100/3.6 has not been studied in patients with severe kidney impairment [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)].

Insulin degludec
No clinically relevant difference in the pharmacokinetics of insulin degludec was identified in a study comparing healthy subjects and subjects with kidney impairment including subjects with end stage kidney disease.

Liraglutide
The safety and efficacy of liraglutide was evaluated in a 26 week clinical study that included patients with moderate kidney impairment (eGFR 30 to 60 mL/min/1.73 m²). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial), [see Clinical Studies (14.1)], 1932 (41.4%) patients had mild kidney impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe kidney impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal kidney function.

There is limited experience with liraglutide in patients with end stage kidney disease. There have been postmarketing reports of acute kidney failure and worsening of chronic kidney failure, which may sometimes require hemodialysis [see Warnings and Precautions (5.7) and Adverse Reactions (6.3)].

8.7 Hepatic Impairment

XULTOPHY 100/3.6

XULTOPHY 100/3.6 has not been studied in patients with hepatic impairment.

Insulin degludec
No clinically relevant difference in the pharmacokinetics of insulin degludec, one of the components of XULTOPHY 100/3.6, was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) [see Clinical Pharmacology (12.3)].
**Liraglutide**

There is limited experience in patients with mild, moderate or severe hepatic impairment with liraglutide, one of the components of XULTOPHY® 100/3.6 (see Clinical Pharmacology (12.3)).

**8.8 Gastroprospses**

Liraglutide, one of the components of XULTOPHY® 100/3.6, slows gastric emptying. XULTOPHY® 100/3.6 has not been studied in patients with pre-existing gastroparesis.

**10 OVERDOSAGE**

Hypoglycemia (not with insulin and liraglutide) and gastrointestinal adverse reactions (from liraglutide) may develop if a patient is dosed with more XULTOPHY® 100/3.6 than required.

An excess of insulin-containing products like XULTOPHY® 100/3.6 relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia. In a healthy volunteer study, the pharmacodynamic effects were similar regardless of whether liraglutide was taken with or without food.

XULTOPHY® 100/3.6 has a pH of approximately 8.15.

**11 DESCRIPTION**

**Insulin degludec**

Insulin degludec is a long-acting basal human insulin analog. Insulin degludec is produced by a process that includes expression of recombiant DNA in Saccharomycyes cerevisiae followed by chemical modification.

Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side-chain consisting of glutamic acid and a C6 fatty acid has been attached (chemical name: LysB29(N-hexadecandioyl-ε-glutamylocysteinylglycine) des(B30) human insulin).

Insulin degludec has a molecular formula of C$_{92}$H$_{148}$N$_{27}$O$_{40}$S$_{24}$ and a molecular weight of 6,104 Da. It has the following structure:

**Figure 1: Structural Formula of Insulin degludec**

**XULTOPHY® 100/3.6 (insulin degludec and liraglutide) injection,** for subcutaneous use, is a combination of a long-acting basal human insulin analog, insulin degludec, and a GLP-1 receptor agonist, liraglutide.

**XULTOPHY® 100/3.6 (insulin degludec and liraglutide) injection,** for subcutaneous use, is a combination of insulin degludec and liraglutide.

**Insulin degludec**

The primary activity of insulin degludec is the regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis.

**Liraglutide**

Liraglutide is a Glucagon-Like Peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.

**12.2 Pharmacodynamics**

Following a single dose administration, XULTOPHY® 100/3.6 has a duration of action reflecting the combination of the individual glucodynamic action profiles of insulin degludec and liraglutide.

Following once-daily administration, XULTOPHY® 100/3.6 lowers fasting plasma glucose levels and postprandial glucose levels.

**Cardiac Electrophysiology (QTc)**

XULTOPHY® 100/3.6 on QTc has not been studied.

**Liraglutide**

The effect of liraglutide, one of the components of XULTOPHY® 100/3.6, on cardiac repolarization was tested in a QTc study. Liraglutide, at steady state concentrations with daily doses up to 1.8 mg, did notproduce QTc prolongation.

**12.3 Pharmacokinetics**

Overall, the pharmacokinetics of insulin degludec and liraglutide were not affected in a clinically relevant manner when administered as XULTOPHY® 100/3.6.

**Absorption**

In patients with type 2 diabetes (mean body weight 87.5 kg) reaching the maximum daily dose (50 units/1.8 mg) of XULTOPHY® 100/3.6, the estimated mean steady-state exposure (AUC 0-24 h) of insulin degludec was 113 nU/mL and of liraglutide 1227 ng/mL based on population pharmacokinetic analysis. The corresponding maximum concentrations were 5.96 µmol/L for insulin degludec and 55 ng/mL for liraglutide. Steady state concentrations of insulin degludec are reached after 2-3 days of daily administration.

**DISTRIBUTION**

Insulin degludec and liraglutide are extensively bound to plasma proteins >99% and >86%, respectively.

**Metabolism**

**Insulin degludec**

Degradation of insulin degludec is similar to that of human insulin; all metabolites formed are inactive.

**Liraglutide**

During the initial 24 hours following administration of a single [4h]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

**Elimination**

The half-life of insulin degludec is approximately 25 hours and the half-life of liraglutide is approximately 13 hours.

**Specific Populations**

**Geriatrics**

Age had no clinically relevant effect on the pharmacokinetics of XULTOPHY® 100/3.6 based on results from a population pharmacokinetic analysis including adult patients up to 83 years treated with XULTOPHY® 100/3.6 (see Use in Specific Populations (8.5)).

**Gender, race and ethnicity**

Gender, race and ethnicity had no clinically relevant effect on the pharmacokinetics of XULTOPHY® 100/3.6 based on results from a population pharmacokinetic analysis.

**Body weight**

The effect of body weight on the exposure level of the components of XULTOPHY® 100/3.6 was investigated in a pharmacokinetic study including adult patients up to 83 years treated with XULTOPHY® 100/3.6. Body weight was not a significant predictor of exposure to insulin degludec and liraglutide.

**Renal Impairment**

XULTOPHY® 100/3.6

There is limited experience with XULTOPHY® 100/3.6 in patients with mild and moderate renal impairment. XULTOPHY® 100/3.6 has not been studied in patients with severe renal impairment (see Warnings and Precautions (5.7)).

**Hepatic impairment**

XULTOPHY® 100/3.6

XULTOPHY® 100/3.6 has not been studied in patients with hepatic impairment.

**Insulin degludec**

Insulin degludec has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single dose (0.4 U/kg) of insulin degludec. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No clinically relevant differences in the pharmacokinetics of insulin degludec were identified between healthy subjects and subjects with hepatic impairment (see Hepatic Impairment (8.7)).

**Liraglutide**

The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score >9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe hepatic impairment was on average 35%, 19%, 29% and 30% lower, respectively (see Warnings and Precautions (5.7)).

**Drug interactions**

**In vitro assessment of drug-drug interactions**

In vitro data suggest that the potential for pharmacokinetic drug interactions related to CYP interaction and protein binding is low for both the liraglutide and insulin degludec components of XULTOPHY® 100/3.6.

The delay of gastric emptying with liraglutide one of the components of XULTOPHY® 100/3.6 may influence absorption of concomitantly administered products. Interactions studies did not show any clinically relevant delay of absorption.

**In vivo assessment of drug-drug interactions**

Liraglutide

The drug-drug interaction studies were performed at steady state with liraglutide 1.8 mg/day. Before administration of concomitant treatment, subjects underwent a 0.6 mg weekly dose increase to their maximum daily dose (50 units/1.8 mg). Administration of the interacting drugs was timed so that Cmax of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

**Dipotassium**

A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide at steady state. The concomitant administration of liraglutide resulted in a reduction of digoxin AUC by 16% and Cmax decreased by 31%. Digoxin median time to maximal concentration was 5.5 hours. The single-dose pharmacokinetics of liraglutide were not affected in a clinically relevant manner when administered as XULTOPHY® 100/3.6.

**Lisinopril**

A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide at steady state. Lisinopril median tmax was delayed from 6 to 8 hours with liraglutide.

**Arotavastatin**

Liraglutide did not change the overall exposure (AUC) of arotavastatin following a single dose of arotavastatin 40 mg, administered 5 hours after the dose of liraglutide at steady state. Arotavastatin Cmax was decreased by 38% and median tmax was delayed from 1 to 3 hours with liraglutide.
Liraglutide did not change the overall exposure (AUC) of acetonaminophen following a single dose of acetonaminophen 1000 mg, administered 8 hours after the dose of liraglutide at steady state. Acetonaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin
Liraglutide did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with liraglutide at steady state. Griseofulvin C_{max} increased by 37% with only median T_{max} change.

Oral Contraceptives
A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} and AUC by 12% and 13%, respectively. There was no impact of liraglutide on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel AUC by 18%. Liraglutide delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

XULTOPHY® 100/3.6
No studies have been conducted with the XULTOPHY® 100/3.6 combination to evaluate the carcinogenic potential, mutagenic or impairment of fertility. The following data are based upon studies with insulin degludec and liraglutide individually.

Insulin degludec
Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study including human insulin (NPH insulin) as comparator, Sprague-Dawley rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 U/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 U/kg/day. Human insulin was dosed at 6.7 U/kg. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary glandular tissues from rats dosed with insulin degludec; and no treatment-related changes in the female mammary gland cell proliferation were found using BrDU incorporation. Further, no treatment related changes in the occurrence of hyperplasia, benign or malignant tumors were recorded in any animals dosed with insulin degludec when compared to vehicle or human insulin.

Genotoxicity testing of insulin degludec was not performed. In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin degludec up to 21 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75 U/kg following a 100/3.6 subcutaneous injection per body surface area) prior to mating and in female rats during gestation had no effect on mating performance and fertility.

Liraglutide
A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day of liraglutide administered by subcutaneous injection at 0.75% of the systemic exposures 0.2-, 2-, 10- and 45-times the human exposure, respectively, at the MRHD of 1.8 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1.0 and 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in rats. The dorsal skin and subcutis, the body surface used for drug injection, was the most common tumor site. Liraglutide treatment with incidences of 0.75% to 8.75% in males and 0.75% to 3.75% in females at the 1.0 mg/kg/day dose. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The high level local concentration of liraglutide was 10-times higher than the concentration in the formulation used for injection. In a 52-week study including human insulin (NPH insulin) as comparator, Sprague-Dawley rats were dosed subcutaneously with liraglutide at 100/3.6 and insulin degludec 100/3.6 mg/kg/day, resulting in 10-times higher concentration of drug near the injection site. These fibrosarcomas were attributed to the high local concentration of drug near the injection site.

Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. Three studies were conducted in patients converting from liraglutide to insulin degludec based on pre-specified non-inferiority margin difference [95% CI].

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-inferiority</th>
<th>p-value</th>
<th>Study</th>
<th>Non-inferiority</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01336022</td>
<td>Total (N)</td>
<td>Placebo + metformin</td>
<td>280</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>79</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Trial (LS Mean)</td>
<td>6.5</td>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline (LS Mean)</td>
<td>-1.42</td>
<td>-0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated treatment difference (95% CI)</td>
<td>-0.81 [-0.98, -0.63]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c ≤ 7%</td>
<td>70.9%</td>
<td>26.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Baseline</td>
<td>164</td>
<td>165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Trial (LS Mean)</td>
<td>118</td>
<td>152</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline (LS Mean)</td>
<td>-46.2</td>
<td>-12.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Results of a 26-Week Trial with XULTOPHY® 100/3.6 in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin Alone or in Combination with Metformin

Liraglutide did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg/kg/day and insulin degludec/0.36 mg liraglutide. The starting dose of insulin degludec was 10 units. XULTOPHY® 100/3.6 was started at 10 units (10 units insulin degludec/0.36 mg liraglutide) and titrated twice weekly towards a target fasting blood glucose goal of 72-108 mg/dL. Patients continued on pre-treatment with sulfonylurea, with or without metformin throughout the trial.

**p<0.001. Primary endpoint was tested for superiority of XULTOPHY® 100/3.6 to placebo.** **p<0.01. Primary endpoint was tested for non-inferiority of XULTOPHY® 100/3.6 to insulin degludec based on pre-specified non-inferiority margin difference [95% CI] and baseline response as covariate.**
Table 7: Results of a 26-Week Trial in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on SGLT2i Alone or in Combination with Metformin, Pioglitazone, and/or DPP4 Inhibitor

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6</th>
<th>Insulin Glargine U-100/3.6</th>
<th>Total (N)</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.2</td>
<td>171</td>
<td>7.8</td>
<td>169</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>6.4</td>
<td>171</td>
<td>7.4</td>
<td>153</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-1.36</td>
<td>171</td>
<td>-0.36</td>
<td>-10.9</td>
</tr>
</tbody>
</table>

a Test for superiority evaluated at 0.05 level for significance. (p<0.0001)
b Estimated using an aCOVA with treatment, pre-trial and region as factors and baseline value as covariate. Multiple imputation modelled “jump to control” of the treatment effect for subjects having missing week 26 data.

Table 8: Results of a 26-Week Trial with XULTOPHY® 100/3.6 in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Insulin U-100/3.6 and Metformin

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6</th>
<th>Insulin Glargine U-100/3.6</th>
<th>Total (N)</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.7</td>
<td>178</td>
<td>7.8</td>
<td>178</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>6.4</td>
<td>178</td>
<td>7.4</td>
<td>155</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-1.32</td>
<td>178</td>
<td>-0.36</td>
<td>-10.9</td>
</tr>
</tbody>
</table>

Patients with missing HbA1c data at week 26 were considered non-responders. There were 5.2% of subjects in the XULTOPHY® 100/3.6 arm for whom HbA1c data was missing at week 26.

Figure 3: Mean HbA1c (%) by Treatment Week in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Insulin Glargine

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6</th>
<th>Insulin Glargine U-100/3.6</th>
<th>Total (N)</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.2</td>
<td>184</td>
<td>7.8</td>
<td>184</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>6.4</td>
<td>184</td>
<td>7.4</td>
<td>158</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-1.36</td>
<td>184</td>
<td>-0.36</td>
<td>-10.9</td>
</tr>
</tbody>
</table>

Patients with missing HbA1c data at week 26 were considered non-responders. There were 6.2% of subjects in the XULTOPHY® 100/3.6 arm for whom HbA1c data was missing at week 26.

Table 9: Results of a 26-Week Trial in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6</th>
<th>Insulin degludec*</th>
<th>Total (N)</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.7</td>
<td>178</td>
<td>7.8</td>
<td>178</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>6.9</td>
<td>178</td>
<td>7.7</td>
<td>156</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-1.05</td>
<td>178</td>
<td>-1.05</td>
<td>-12.6</td>
</tr>
</tbody>
</table>

Patients with missing HbA1c data at week 26 were considered non-responders. There were 11.1% of subjects in the XULTOPHY® 100/3.6 arm and 13.1% in the insulin degludec arm for whom HbA1c data was missing at week 26.

Table 10: Summary of Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insulin degludec*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Male 52%</td>
<td>0.05</td>
</tr>
<tr>
<td>Race (%)</td>
<td>White 92%</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>12.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Patients could not increase the dose of insulin degludec by more than 4 units per week, and the maximum dose of insulin glargine was limited to 50 units. The targeted fasting blood glucose goal was achieved in 24.0% of patients randomized to insulin glargine and in 31.6% of the patients randomized to XULTOPHY® 100/3.6 at 26 weeks.

At the end of 26 weeks, reductions in HbA1c, from baseline of 1.94% for XULTOPHY® 100/3.6 and 1.05% for insulin glargine limited to 50 units daily were observed (see Table 9). The mean difference (95% CI) in HbA1c reduction between XULTOPHY® 100/3.6 and insulin degludec was -0.89 [-1.10, -0.68] and statistically significant. The trial was designed to show the contribution of the liraglutide component to glycemic lowering and the insulin degludec dosing algorithm was selected to isolate the effect of the GLP-1 component. At the end of the trial, the doses of insulin degludec were equivalent between treatment groups. The mean final dose of XULTOPHY® 100/3.6 and insulin degludec was 46 units (for XULTOPHY® 100/3.6: 46 units insulin degludec/1.66 mg liraglutide). The difference in glucose lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the caresetting where alternative insulin degludec dosages can be used.

A Maximum dose 50 units

b Estimated using an aCOVA with treatment, country, and previous antidiabetic treatment as fixed factors and baseline response as covariate. Multiple imputation modelled “jump to control” of the treatment effect for subjects having missing week 26 data.

c Patients with missing HbA1c data at week 26 were considered non-responders. There were 11.1% of subjects in the XULTOPHY® 100/3.6 arm and 13.1% in the insulin degludec arm for whom HbA1c data was missing at week 26.

Xultophy® 100/3.6 (insulin degludec and liraglutide) injection
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XULTOPHY® 100/3.6 (insulin degludec and liraglutide) is an injection supplied as a clear, colorless solution in a 3 mL pre-filled, disposable, single-patient use pen injector. The XULTOPHY® 100/3.6 pen (100 units/mL insulin degludec and 3.6 mg/mL liraglutide) is a disposable, single-patient use pen injector. The XULTOPHY® 100/3.6 pen consists of a needle assembly, pen body, and an integrated Liraglutide Prefilled Injection (100 units/mL insulin degludec and liraglutide) injection component. The XULTOPHY® 100/3.6 pen contains 100 units/mL insulin degludec and 3.6 mg/mL liraglutide. The XULTOPHY® 100/3.6 pen can be used for insulin degludec and liraglutide injection via the disposable, single-patient use pen injector.

Dosage Unit/Strength

3 mL single-patient-use XULTOPHY® 100/3.6 pen (100 units/mL insulin degludec and 3.6 mg/mL liraglutide)

Table 10: Results of a 26-Week Trial in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Insulin Glargine U-100

<table>
<thead>
<tr>
<th>XULTOPHY® 100/3.6 + metformin</th>
<th>Insulin glargine U-100 + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (N)</strong></td>
<td>278</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>219</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>8.4</td>
</tr>
<tr>
<td><strong>End of Trial (LS Mean)</strong></td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Change from baseline (LS Mean)</strong></td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Estimated treatment difference (95% CI)</strong></td>
<td>-1.67</td>
</tr>
<tr>
<td><strong>Percentage of patients achieving HbA1c &lt;7%</strong></td>
<td>68.3%</td>
</tr>
<tr>
<td><strong>TPG (mg/dL)</strong></td>
<td>160</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>160</td>
</tr>
<tr>
<td><strong>End of Trial (LS Mean)</strong></td>
<td>110</td>
</tr>
<tr>
<td><strong>Change from baseline (LS Mean)</strong></td>
<td>-49.9</td>
</tr>
</tbody>
</table>

16.2 Recommended Storage

Dispense in the original sealed carton with the enclosed Instructions for Use. Prior to first use, XULTOPHY® 100/3.6 should be stored between 2°C and 8°C (36°F to 46°F) until the expiration date printed on the label. Store prefilled pens in the carton so they will stay clean and protected from light. Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use XULTOPHY® 100/3.6 pens that have been frozen.

After first use, the XULTOPHY® 100/3.6 pen can be stored for 21 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep all XULTOPHY® 100/3.6 pens away from direct heat and light. Always remove the needle after each injection and store the XULTOPHY® 100/3.6 pen without a needle attached. This prevents contamination and/or leakage, of the XULTOPHY® 100/3.6 pen, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

The storage conditions are summarized in Table 11:

Table 11: Storage Conditions for XULTOPHY® 100/3.6 Pen

<table>
<thead>
<tr>
<th>Prior to first use</th>
<th>After first use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>36°F to 46°F</td>
<td>59°F to 86°F</td>
</tr>
<tr>
<td>(2°C to 8°C)</td>
<td>(15°C to 30°C)</td>
</tr>
<tr>
<td>Refrigorated</td>
<td>Refrigerated</td>
</tr>
<tr>
<td>36°F to 46°F</td>
<td>36°F to 46°F</td>
</tr>
<tr>
<td>(2°C to 8°C)</td>
<td>(2°C to 8°C)</td>
</tr>
<tr>
<td>Until expiration date</td>
<td>21 Days</td>
</tr>
</tbody>
</table>

Advertise patients that the administration of more than 50 units of XULTOPHY® 100/3.6 daily can result in overdose of the liraglutide component. Instruct patients not to administer concurrently with other glucagon-like peptide-1 receptor agonists.

Hyperglycemia or Hyperglycemia

Inform patients that hyperglycemia is the most common adverse reaction with insulin products. Inform patients of the symptoms of hyperglycemia (e.g. impaired ability to concentrate and react). This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advise patients with frequent hypoglycemia or reduced or absent warning signs of hyperglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hyperglycemia and that changes in insulin regimen should be made under close medical supervision [see Warnings and Precautions (5.4)].

Never Share a XULTOPHY® 100/3.6 Pen Between Patients

Advise patients that they must never share a XULTOPHY® 100/3.6 pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of liraglutide, one of the components of XULTOPHY® 100/3.6. If symptoms of hypersensitivity reactions occur, patients must stop taking XULTOPHY® 100/3.6 and seek medical advice promptly [see Warnings and Precautions (5.8)].

Hepatobiliary Disorders

Inform patients that hepatobiliary disorders including elevations of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant [see Use in Specific Populations (8.1)].

For information about XULTOPHY® 100/3.6 contact: Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500 (Se habla español)
www.novonordisk-us.com

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Manufactured by:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
U.S. License Number 1261

For information about XULTOPHY® 100/3.6 contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-800-727-6500 (Se habla español)
www.novonordisk-us.com
What is XULTOPHY® 100/3.6? 

XULTOPHY® 100/3.6 is an injectable prescription medicine that contains 2 diabetes medicines, insulin degludec, 100 units/mL, and liraglutide, 3.6 mg/mL. XULTOPHY® 100/3.6 should be used along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes mellitus.

XULTOPHY® 100/3.6 is not recommended as the first choice of medicine for treating diabetes.

You should not use XULTOPHY® 100/3.6 if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are pregnant or breastfeeding. It is not known if XULTOPHY® 100/3.6 can be used with mealtime insulin.
- you are allergic to insulin degludec, liraglutide or any of the ingredients in XULTOPHY® 100/3.6.
- you have had an allergic reaction to a GLP-1 receptor agonist medicine.
- Do not use XULTOPHY® 100/3.6 if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Tell your health care provider before using XULTOPHY® 100/3.6 if:

- you have or have had problems with your pancreas, kidneys, or liver.
- you have heart failure or other heart problems. If you have heart failure, it may get worse while you take XULTOPHY® 100/3.6.
- you have problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digestive food.
- you are taking medicines called GLP-1 receptor agonists.
- you are pregnant or plan to become pregnant. It is not known if XULTOPHY® 100/3.6 will harm your unborn baby. Tell your health care provider if you become pregnant or think you may be pregnant while using XULTOPHY® 100/3.6.
- you are breastfeeding or plan to breastfeed. It is not known if XULTOPHY® 100/3.6 passes into your breast milk. Talk to your health care provider about the best way to feed your baby while using XULTOPHY® 100/3.6.
- you have had an allergic reaction to a GLP-1 receptor agonist medicine.
- you are taking insulin degludec, liraglutide or any of the other medicines that work like liraglutide caused thyroid tumors, including thyroid cancer. It is not known if XULTOPHY® 100/3.6 will cause thyroid tumors in people.

Tell your health care provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XULTOPHY® 100/3.6 may affect the way some medicines work, and some medicines may affect the way XULTOPHY® 100/3.6 works. Before using XULTOPHY® 100/3.6, talk to your health care provider about low blood sugar and how to manage it. Tell your health care provider if you are taking other diabetes medicines that can cause low blood sugar.

How should I use XULTOPHY® 100/3.6? 

Read the Instructions for Use that comes with XULTOPHY® 100/3.6.

Use XULTOPHY® 100/3.6 exactly as your health care provider tells you to use it.

Do not change your dosing schedule without first talking to your health care provider. The dose counter on your XULTOPHY® 100/3.6 pen shows the number of units of XULTOPHY® 100/3.6 to be injected.

Your health care provider should show you how to use XULTOPHY® 100/3.6 before you use it for the first time.

XULTOPHY® 100/3.6 is injected under the skin (subcutaneously) of your thigh, upper arm or stomach (abdomen).

Do not inject XULTOPHY® 100/3.6 into a vein (intravenously) or use in an insulin infusion pump.

Use XULTOPHY® 100/3.6 at the same time each day with or without food.

What is the most important information I should know about XULTOPHY® 100/3.6? 

XULTOPHY® 100/3.6 may cause serious side effects, including:

- Possible thyroid tumors, including cancer. Tell your health care provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, liraglutide, one of the components of XULTOPHY® 100/3.6, and medicines that work like liraglutide caused thyroid tumors, including thyroid cancer. It is not known if XULTOPHY® 100/3.6 will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people.
- Do not use XULTOPHY® 100/3.6 if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Possible side effects include:

- chest pain or tightness
- problems breathing or swallowing
- slurred speech
- hives
- swelling of your face, lips, tongue, or throat
- rash
- itching
- fast heartbeat
- fainting or feeling dizzy
- gallbladder problems. Gallbladder problems have happened in some people who take XULTOPHY® 100/3.6. Tell your health care provider right away if you have symptoms of gallbladder problems, which may include:
  - pain in your upper stomach (abdomen)
  - yellowing of skin or eyes (jaundice)
  - fever
  - clay-colored stools
- low potassium in your blood (hypokalemia).
- heart failure. Taking certain diabetes pills called thiazolidinediones or TZDs with XULTOPHY® 100/3.6 may cause heart failure in some people. This can happen even if you have never had heart failure before. If you already have heart failure, it may get worse while you take XULTOPHY® 100/3.6.
- kidney problems (kidney failure). Worsening of kidney failure and sudden kidney failure have happened in some people who take XULTOPHY® 100/3.6.
- Worsening of kidney failure and sudden kidney failure have happened in some people who take XULTOPHY® 100/3.6.
- Check the Pen label each time you give your injection to make sure you are using the correct medicine.
- Do not take more than 50 units of XULTOPHY® 100/3.6 each day. XULTOPHY® 100/3.6 contains two medicines: insulin degludec and liraglutide. If you take too much XULTOPHY® 100/3.6, it can cause severe nausea and vomiting.
- Check your blood sugar levels. Ask your health care provider what your blood sugars should be and when you should check your blood sugar levels.
- Change (rotate) your injection sites within the area you choose with each injection to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- Do not use XULTOPHY® 100/3.6 with another medicine that can cause low blood sugar.
- Signs and symptoms of low blood sugar may include:
  - dizziness or light-headedness
  - anxiety, irritability, or mood changes
  - slurred speech
  - confusion or drowsiness
  - weakness
  - fast heartbeat
  - abnormal function of heart
  - numbness or tingling
  - hunger
  - sweating
  - nausea
  - weakness
  - blurred vision
  - swallowing
  - thirst
  - low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use XULTOPHY® 100/3.6 with another medicine that can cause low blood sugar.

What should I avoid while taking XULTOPHY® 100/3.6? 

While taking XULTOPHY® 100/3.6 do not:

- drive or operate heavy machinery, until you know how XULTOPHY® 100/3.6 affects you.
- drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of XULTOPHY® 100/3.6? 

XULTOPHY® 100/3.6 may cause serious side effects that can lead to death, including:

- See “What is the most important information I should know about XULTOPHY® 100/3.6?”
- inflammation of your pancreas (pancreatitis). Stop using XULTOPHY® 100/3.6 and call your health care provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use XULTOPHY® 100/3.6.

Possible side effects include:

- chest pain or tightness
- problems breathing or swallowing
- slurred speech
- hives
- swelling of your face, lips, tongue, or throat
- rash
- itching
- fast heartbeat
- fainting or feeling dizzy
- gallbladder problems. Gallbladder problems have happened in some people who take XULTOPHY® 100/3.6.

Tell your health care provider if you have symptoms of a serious allergic reaction including:

- yellowing of skin or eyes (jaundice)
- fever
- clay-colored stools
- low potassium in your blood (hypokalemia).
- heart failure. Taking certain diabetes pills called thiazolidinediones or TZDs with XULTOPHY® 100/3.6 may cause heart failure in some people. This can happen even if you have never had heart failure before. If you already have heart failure, it may get worse while you take XULTOPHY® 100/3.6.
- kidney problems (kidney failure). Worsening of kidney failure and sudden kidney failure have happened in some people who take XULTOPHY® 100/3.6.
- Worsening of kidney failure and sudden kidney failure have happened in some people who take XULTOPHY® 100/3.6.
The most common side effects of XULTOPHY® 100/3.6 include stuffy or runny nose, sore throat, headache, nausea, diarrhea, increased blood levels of lipase, and upper respiratory tract infection. Talk to your healthcare provider about any side effect that bothers you or does not go away.

These are not all the possible side effects of XULTOPHY® 100/3.6.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Keep XULTOPHY® 100/3.6 and all medicines out of the reach of children.

General information about the safe and effective use of XULTOPHY® 100/3.6.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XULTOPHY® 100/3.6 for a condition for which it was not prescribed. Do not give XULTOPHY® 100/3.6 to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about XULTOPHY® 100/3.6 that is written for health professionals.

What are the ingredients in XULTOPHY® 100/3.6?

**Active Ingredients:** insulin degludec and liraglutide

**Inactive Ingredients:** glycerol, phenol, zinc, and Water for Injection. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

Manufactured by: Novo Nordisk Inc., Plainsboro, NJ 08536, U.S. License Number 1261

For more information, go to www.novonordisk-us.com or call 1-800-727-6500 (Se habla español).

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Instructions for Use
XULTOPHY® 100/3.6 (ZUL-to-fye)
(inulin degludec and liraglutide) injection

Do not share your XULTOPHY® 100/3.6 pen with another person. You may give an infection to them or get an infection from them.

- XULTOPHY® 100/3.6 pen ("pen") is a prefilled disposable, single-patient-use pen containing 300 units of insulin degludec and 10.8 mg of liraglutide (insulin degludec and liraglutide) injection. You can inject doses from 10 to 50 units in a single injection (with each unit of insulin degludec, the pen also delivers 0.036 mg of liraglutide). The dose can be increased by 1 unit at a time. The dose equals the number of units shown in the dose counter.

- People who are blind or have vision problems should not use the pen without help from a person trained to use the pen.

Supplies you will need to give your XULTOPHY® 100/3.6 injection:
- XULTOPHY® 100/3.6 pen
- a sharps container for throwing away used pens and needles.
- alcohol swab
- a new NovoFine or NovoTwist needle
- a drop of XULTOPHY® 100/3.6 is left in your pen:

Preparation your XULTOPHY® 100/3.6 pen:
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the XULTOPHY® 100/3.6 pen label before each use to make sure it is your XULTOPHY® 100/3.6 pen.
- XULTOPHY® 100/3.6 should look clear and colorless. Do not use it if it looks cloudy or colored.
- Do not use XULTOPHY® 100/3.6 past the expiration date printed on the label or 21 days after you start using the pen.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection or get a serious infection from them.

NovoFine®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoTwist®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

XULTOPHY® 100/3.6 pen
- Dose counter
- Dose selector
- Dose button
- Dose pointer
- Pen cap
- Pen scale
- Pen window

Step 1:
- Pull pen cap straight off (See Figure B).

Step 2:
- Check the liquid in the pen (See Figure C). XULTOPHY® 100/3.6 should look clear and colorless. Do not use it if it looks cloudy or colored.

Step 3:
- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).

Step 4:
- Push the capped needle straight onto the pen and twist the needle on until it is tight (See Figure E).

Step 5:
- Pull off the outer needle cap. Do not throw it away (See Figure F).

Step 6:
- Pull off the inner needle cap and throw it away (See Figure G).

Step 7:
- Turn the dose selector to select the priming symbol (---). (See Figure H).

Step 8:
- Hold the pen with the needle pointing up. Tap the top of the pen gently a few times to let any air bubbles rise to the top (See Figure I).

Step 9:
- Hold the pen with the needle pointing up. Press and hold in the dose button until the dose counter shows "0." The "0" must line up with the dose pointer.
- A drop of XULTOPHY® 100/3.6 should be seen at the needle tip (See Figure J).
- If you do not see a drop of XULTOPHY® 100/3.6, repeat steps 7 to 9, no more than 6 times. until a drop of XULTOPHY® 100/3.6 appears at the needle tip.
- If you still do not see a drop of XULTOPHY® 100/3.6, change the needle and repeat steps 7 to 9.

Selecting your dose: Make sure you prime your pen before setting your dose.

Step 10:
- XULTOPHY® 100/3.6 pen is made to deliver the number of units that your healthcare provider prescribed.
- Take your dose exactly as your healthcare provider tells you to.
- Do not change your dose, even if you are having problems with injection, do not use XULTOPHY® 100/3.6, change the needle and repeat steps 7 to 9.

Examples
- 16 units selected
- 27 units selected
- 200 units left

To see how much XULTOPHY® 100/3.6 is left in your pen:
- Turn the dose selector until it stops. The dose counter will line up with the dose pointer.
- If the dose counter shows 50, there is a dose of at least 50 units left in your pen.
- If the dose counter shows between 10 and 50, the number shown in the dose counter is the total units left in your pen.
- If there is not enough XULTOPHY® 100/3.6 left in your pen for a full dose, do not use it. Use a new XULTOPHY® 100/3.6 pen.
Giving your injection:

- Inject your XULTOPHY® 100/3.6 exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- XULTOPHY® 100/3.6 can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs) or upper arms.
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. Do not use the same injection site for each injection. Do not inject where the skin has pits, is thickened, or has lumps. Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Step 11:

- Choose your injection site (stomach, upper legs or upper arms) and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.

Step 12:

- Insert the needle into your skin (See Figure N).
  - Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.

Step 13:

- Press and hold down the dose button until the dose counter shows “0” (See Figure O).
  - The “0” must line up with the dose pointer. You may hear or feel a click.

Step 14:

- Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6 (See Figure P).
  - When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  - If the needle is removed before you count to 6, you may see a stream of XULTOPHY® 100/3.6 coming from the needle tip.
  - If you see a stream of XULTOPHY® 100/3.6 coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more XULTOPHY® 100/3.6.

Step 15:

- Pull the needle out of your skin (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

Step 16:

- Carefully remove the needle from the pen after each use and throw it away (See Figure R).
  - Do not recap the needle. Recapping the needle can lead to needle stick injury.
  - Do not store the pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the pen.

After your injection:

- The used XULTOPHY® 100/3.6 pen may be thrown away in your household trash after you have removed the needle.
- Put your used needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my XULTOPHY® 100/3.6 pen?

Before use:

- Store unused XULTOPHY® 100/3.6 pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze XULTOPHY® 100/3.6. Do not use XULTOPHY® 100/3.6 if it has been frozen.
- Unused pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- If XULTOPHY® 100/3.6 is stored outside of refrigeration prior to first use, it should be used or thrown away within 21 days.
- Store the pens in the carton they come in to keep them clean and protected from light.

Pen in use:

- Store the pen you are currently using at room temperature at 59°F to 86°F (15°C to 30°C) or in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze XULTOPHY® 100/3.6. Do not use XULTOPHY® 100/3.6 if it has been frozen.
- Keep XULTOPHY® 100/3.6 away from heat and light.
- The XULTOPHY® 100/3.6 pen you are using should be thrown away after 21 days, even if it still has XULTOPHY® 100/3.6 left in it and the expiration date has not passed.

General Information about the safe and effective use of XULTOPHY® 100/3.6:

- Keep XULTOPHY® 100/3.6 pens and needles out of the reach of children.
- Always use a new needle for each injection.

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For additional information about Xultophy™ 100/3.6 go to: www.Xultophy10036.com

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For more information call Novo Nordisk at 1-800-727-6500

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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