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.

WARNINGS AND PRECAUTIONS

• 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).

Recent Major Changes

Indications and Usages (1)............................................. 02/2019
Dosage and Administration (2.2, 2.3).......................... 02/2019
Contraindications (4)............................................. 02/2019
Warnings and Precautions (5.2, 5.4, 5.8, 5.9)............ 02/2019

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.

Limitations of Use (1):

• Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.

• 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 (2.2).

• Recommended starting dose in patients naïve to basal insulin or GLP-1 receptor agonist is 10 units (10 units of insulin degludec and 0.36 mg of liraglutide) given subcutaneously once-daily (2.2).

• Recommended starting dose in patients currently on basal insulin or GLP-1 receptor agonist is 16 units (16 units of insulin degludec and 0.56 mg of liraglutide) given subcutaneously once-daily (2.2).

• 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).

• See Full Prescribing Information for titration recommendations (2.3).

• Inject subcutaneously in thigh, upper arm or abdomen (2.5).

• Do not administer intravenously, intramuscularly, or by an infusion pump (2.5).

• Do not dilute or mix with any other insulin products or solutions (2.5).

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).

• During episodes of hypoglycemia (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).

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).

• Hypo- or hyperglycemia with changes in XULTOPHY® 100/3.6, monitor. Carry out 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 care (5.8).

• Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.9).

• Hypokalemia: May be life-threatening. Monitor potassium levels and 1.8 mg of liraglutide) (2.1).

• Do not administer intravenously, intramuscularly, or by an injection pump (2.5).

• Do not dilute or mix with any other insulin products or solutions (2.5).

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 1-800-727-6505 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 (7.7).

• Efects of delayed gastric emptying on oral medications: May impact absorption of concomitantly administered oral medications (7.2).

Use in Special 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: 08/2019

Full Prescribing Information: Contents* Warning: Risk of Thyroid C-Cell Tumors

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5.2 Pancreatitis

5.3 Never Share a XULTOPHY® 100/3.6 Pen Between Patients

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17 Patient Counseling Information

*Sections or subsections omitted from the full prescribing information are not listed.
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 tumour findings to humans [see Warnings and Precautions (5.1)].
• 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 (5.6)].
• 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 (5.1)].

2.2 Recommended Starting Dose
In patients naive 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 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 needs, 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)].

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 [see Adverse Reactions (6.1)].
• 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, intramuscularly, or in an insulin infusion pump.
• Do not dilute or mix XULTOPHY® 100/3.6 with any other insulin products or solutions.
• Do not split the dose of XULTOPHY® 100/3.6.

3  DOSAGE FORMS AND STRENGTHS
XULTOPHY® 100/3.6 injection: 100 units insulin degludec per mL and 3.6 mg liraglutide per mL available as a clear, colorless solution in a 3 mL prefilled, 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 XULTOPHY® 100/3.6, either insulin degludec or liraglutide, or any of its excipients. Serious hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with liraglutide, one of the components of XULTOPHY® 100/3.6 [see Warnings and Precautions (5.8)].

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 (adenomas and/or carcinomas) in clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 will cause 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.
• Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.
XULTOPHY® 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with 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 MT in patients treated with XULTOPHY® 100/3.6. Although no cases of MT have been reported in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6. In glycemic control trials of liraglutide, there have been 13 cases of pancreatitis among liraglutide-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 liraglutide were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a liraglutide-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 cholecystitis or alcohol abuse.

After 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 vomited). 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 development of pancreatitis on liraglutide.

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 infection.

5.4 Hypoglycemia or Hypoglycemia with Changes in XULTOPHY® 100/3.6 Regimen

Changes in XULTOPHY® 100/3.6 regimen may affect glycemic control and predispose to hypoglycemia or hypoglycemia [see Warnings and Precautions (5.5)]. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. Adjustments to concomitant 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 ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). XULTOPHY® 100/3.6 (an insulin-containing product) or any insulin, should not be used during episodes of hypoglycemia [see Contraindications (4)].

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, or in patients with a higher risk for hypoglycemia and patients who have reduced sym pathetic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.7 Acute Kidney Injury

There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6 [see Adverse Reactions (6.3)]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

5.8 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur with XULTOPHY® 100/3.6. Allergic reactions (manifested with signs and symptoms such as urticaria, rash, pruritus) have been reported with XULTOPHY® 100/3.6. There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide, one of the components of XULTOPHY® 100/3.6 [see Adverse Reactions (6.3)]. If a hypersensitivity reaction occurs, discontinue XULTOPHY® 100/3.6; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with XULTOPHY® 100/3.6. XULTOPHY® 100/3.6 is contraindicated in patients who have had hypersensitivity reactions to another GLP-1 receptor agonist. Some of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thrombosis—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 and Allergic 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. The mean age was 57 years and 2.8% were older than 75 years; 52.6% were male, 75.0% were White, 6.2% were Black or African American and 15.9% were Hispanic or Latino. The mean body mass index (BMI) was 31.8 kg/m$^2$. The mean duration of diabetes was 8.7 years and the mean HbA1c at baseline was 8.2%. A history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported in 25.4%, 12.0%, 6.5% and 6.3% respectively. The mean estimated glomerular filtration rate (eGFR) at baseline was 88.3 mL/min/1.73 m$^2$ and 6.2% of the patients had an eGFR less than 60 mL/min/1.73 m$^2$.

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>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</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 is the most commonly observed adverse reaction in patients using insulin and insulin containing products, including XULTOPHY® 100/3.6 [see Warnings and Precautions (5.6)]. The number of reported hypoglycemia episodes depends on the definition of hypoglycemia used, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for XULTOPHY® 100/3.6 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the phase 3 clinical program [see Clinical Studies (14)], events of severe hypoglycemia were defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (Table 4). Hypoglycemia episodes with a glucose level below 54 mg/dL associated with or without symptoms is shown in Table 4. No clinically important differences in risk of severe hypoglycemia between XULTOPHY® 100/3.6 and comparators were observed in clinical trials.
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><strong>XULTOPHY® 100/3.6</strong></td>
<td><strong>XULTOPHY® 100/3.6</strong></td>
<td><strong>XULTOPHY® 100/3.6</strong></td>
</tr>
<tr>
<td>NCT01330022</td>
<td>NCT01619162</td>
<td>NCT02773468</td>
</tr>
<tr>
<td><strong>NCT01675116</strong></td>
<td><strong>NCT01392573</strong></td>
<td><strong>NCT0152145</strong></td>
</tr>
<tr>
<td>Total Subjects (N)</td>
<td>285</td>
<td>288</td>
</tr>
<tr>
<td>Severe Hypoglycemia (%)</td>
<td>0.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1. Hypoglycemia with a glucose level below 54 mg/dL (%)

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, abdominal pain, flatulence, eructation, gastroesophageal reflux disease, abdominal distension and decreased appetite have been reported in patients treated with XULTOPHY® both on- and off-label use. The incidence of cholelithiasis was more frequent at the beginning of XULTOPHY® 100/3.6 therapy and diminished 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 glycemic control trials of liraglutide, the incidence of cholelithiasis was 0.3% in both liraglutide-treated and placebo-treated patients.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, anaphylactoid, bronchospasm, hypotension, and shock may occur with any insulin-containing products including XULTOPHY® 100/3.6 and may be life-threatening (see Warnings and Precautions (5.1)). Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness, and itching) and urticaria were reported.

Vital signs

**Lipidostrophy**

Long-term use of insulin containing products, including XULTOPHY® 100/3.6, can cause lipidostrophy at the site of repeated injections. Lipidostrophy includes lipohypertrophy (thickening of adipose tissue) and lipodystrophy (thinning of adipose tissue), and may affect absorption [see Dosage and Administration (2.5)].

Peripheral Edema

Insulin containing products, including 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 insulin. 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, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, 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.

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>
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<td>285</td>
<td>288</td>
</tr>
<tr>
<td>Severe Hypoglycemia (%)</td>
<td>0.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1. Hypoglycemia with a glucose level below 54 mg/dL that are associated with or without symptoms of hypoglycemia.

**Xultophy® 100/3.6 (insulin degludec and liraglutide injection)**

Administration of XULTOPHY® 100/3.6 may cause formation of antibodies against insulin degludec and/or liraglutide. In rare cases, the presence of such antibodies may necessitate adjustment of the dosage of the XULTOPHY® 100/3.6 dose in order to correct a tendency to hyper- or hypoglycemia. In the clinical trials where antibodies were measured in patients receiving XULTOPHY® 100/3.6, 11.1% of patients were positive for insulin degludec specific antibodies at end of treatment vs. 2.4% at baseline. 50.8% of patients were positive for antibodies cross-reacting with human insulin at end of treatment vs. 14.6% at baseline. 2.1% of patients were positive for anti-liraglutide antibodies at end of treatment (no patients were positive at baseline). Antibody formation has not been associated with reduced efficacy of XULTOPHY® 100/3.6.

VICTOZA® (liraglutide)

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with liraglutide may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to XULTOPHY® 100/3.6 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the double-blind 52-week monotherapy trial and in the double-blind 26-week add-on combination therapy trials, antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 2.3% of the liraglutide-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide 1 (GLP-1) occurred in 6.9% of the liraglutide-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the liraglutide-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 2.3% of the liraglutide-treated patients. The incidence of anti-liraglutide antibodies was 0.7% in the double-blind 26-week add-on combination therapy trials. Antibody formation was not associated with reduced efficacy of liraglutide when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with liraglutide treatment.

In five double-blind glycemic control trials of liraglutide, events from a composite of adverse events potentially related to immunogenicity (eg. urticaria, angioedema) occurred among 0.8% of liraglutide-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for liraglutide-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity events composite than were patients who did not develop anti-liraglutide antibodies.

In a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) liraglutide-treated patients with antibody measurements. Of the 11 liraglutide-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies to native glucagon-like peptide 1 (GLP-1).

TREGISBA® (insulin degludec)

In a 52-week study of adult insulin-naïve type 2 diabetes patients, 1.7% of patients who received insulin degludec were positive at baseline for anti-insulin degludec antibodies and 6.2% of patients developed anti-insulin degludec antibodies at least once during the study. In these trials, between 90.7% and 99.7% of patients who were positive for insulin degludec antibodies were also positive for anti-human insulin antibodies.

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
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, animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures 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].

The estimated background risk for major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to increase to about 13–20% for women with an HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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, embryofetal development and pre- and postnatal 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-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossificaciones and/or skeletal abnormalities occurred in all treated groups. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeded concurrent and historical controls were misshapen pharynx and/or narrowed oral cavity and/or larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/kg at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart), 0.05 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tibia, fibula, sterno-clavicular joint and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8–, 3-, and 11-times human exposure at the MRHD of 1.8 mg/kg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior sometimes resulted in death. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior sometimes followed by hyperglycemia. Pentamidine may cause hypoglycemia, which may require monitoring when XULTOPHY is co-administered with these drugs.

Nonetheless, caution should be exercised when oral medications are concomitantly administered with liraglutide-containing products. (see Clinical Pharmacology (12.3))

In elderly 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 the elderly.

8.6 Renal Impairment XULTOPHY 100/3.6

There is limited experience with XULTOPHY 100/3.6 in patients with and without renal impairment and when used in these patients, additional glucose monitoring and XULTOPHY 100/3.6 dose adjustments may be required on an individual basis. XULTOPHY 100/3.6 has not been studied in patients with severe renal 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 renal impairment including subjects with end stage renal disease.

Liraglutide

The safety and efficacy of liraglutide was evaluated in a 26 week study that included 20–25% in women with chronic renal failure, on dialysis, or requiring hemodialysis (eGFR 30 to 60 ml/min/1.73 m²). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], 1932 (5.2%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with liraglutide in patients with end stage renal disease. There have been postmarketing reports of acute renal failure in patients with chronic renal failure, on dialysis, or requiring hemodialysis (eGFR 30 to 60 ml/min/1.73 m²). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], 1932 (5.2%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with liraglutide in patients with end stage renal disease. There have been postmarketing reports of acute renal failure in patients with chronic renal failure, on dialysis, or requiring hemodialysis (eGFR 30 to 60 ml/min/1.73 m²). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], 1932 (5.2%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. There is limited experience with liraglutide in patients with end stage renal disease. There have been postmarketing reports of acute renal failure in patients with chronic renal failure, on dialysis, or requiring hemodialysis (eGFR 30 to 60 ml/min/1.73 m²). In the liraglutide treatment arm of a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], 1932 (5.2%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.
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.

10 OVERDOSAGE

Hypoglycemia (from 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 life-threatening hypoglycemia and hypokalemia [see Warnings and Precautions (5.6, 5.10)]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recrudescence of hypoglycemia. Hypokalemia must be corrected appropriately.

Overdoses have been reported in clinical trials and postmarketing use of liraglutide, one of the components of XULTOPHY® 100/3.6. Effects have included severe nausea and severe vomiting. In the event of overdose, appropriate supportive treatment should be initiated according to the patient’s clinical signs and symptoms.

11 DESCRIPTION

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.

Insulin degludec

Insulin degludec is a long-acting basal human insulin analog. Insulin degludec is produced by a process that includes expression of recombinant DNA in Saccharomyces 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 C16 fatty acid has been attached (chemical name: LysB29(Nε-hexadecanoic)γ-Glu (B30) human insulin). Insulin degludec has a molecular formula of C3331H5176O955N65S50 and a molecular weight of 6103.97. It has the following structure:

Figure 1: Structural Formula of Insulin degludec

Liraglutide

Liraglutide is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C16 fatty acid (palmitic acid) with a glutamic acid side chain on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C262H362O92N6S4O3 and the molecular weight is 3751.2 Daltons. The structural formula (Figure 2) is:

Figure 2: Structural Formula of Liraglutide

XULTOPHY® 100/3.6 is sterile, aqueous, clear, and colorless solution. Each pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 3.6 mg liraglutide. XULTOPHY® 100/3.6 contains the following inactive ingredients per mL: glycerol 19.7 mg, phenol 5.70 mg, zinc 55 mg, and water for injection. XULTOPHY® 100/3.6 has a pH of approximately 8.15. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XULTOPHY® 100/3.6

XULTOPHY® 100/3.6 is a combination product consisting of insulin degludec and liraglutide.

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12 CLINICAL PHARMACOLOGY

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XULTOPHY® 100/3.6 is a combination product consisting of insulin degludec and liraglutide.
The efficacy and safety of XULTOPHY 100/3.6 for both ethinylestradiol and levonorgestrel by 1.5 hours. The mean BMI was 31.2 kg/m² compared to placebo (see -0.81% [-0.98; -0.63] max). -1.21 # 1c with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A dose-related increase in benign thyroid C-cell adenomas was seen on the dorsal skin and throughout mating until gestation day 17. No direct adverse effects on male fertility were observed at dosages up to 1.5 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the human exposure at the MRHD based on plasma AUC comparison. In female Sprague-Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/kg). Multiple imputation modelled “jump-to-control” of the treatment effect for subjects having missing week 26 data. **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 of 0.3% and for superiority of XULTOPHY 100/3.6 to liraglutide. *Estimated using an ANCOVA with treatment, baseline HbA1c, stratum, sub-study, concomitant diabetes treatment and country as factors and baseline response as covariate. Multiple imputation modelled “return to baseline” of the treatment effect for subjects having missing week 26 data. **p<0.001. Primary endpoint was tested for superiority of XULTOPHY 100/3.6 to placebo. *Patients with missing HbA1c value at week 26 data were considered non-responders. There were 12.6% of subjects in the XULTOPHY 100/3.6 arm, 12.3% in the insulin degludec arm and 15.5% in the liraglutide arm for whom HbA1c was data missing at week 26. Table 5: 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 combination with metformin. 0.075 U/kg/day. No direct adverse effects on male fertility were observed at dosages up to 1.5 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the human exposure at the MRHD based on plasma AUC comparison. In female Sprague-Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/kg). Multiple imputation modelled “jump-to-control” of the treatment effect for subjects having missing week 26 data. **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 of 0.3% and for superiority of XULTOPHY 100/3.6 to liraglutide. *Estimated using an ANCOVA with treatment, baseline HbA1c, stratum, sub-study, concomitant diabetes treatment and country as factors and baseline response as covariate. Multiple imputation modelled “return to baseline” of the treatment effect for subjects having missing week 26 data. **p<0.001. Primary endpoint was tested for superiority of XULTOPHY 100/3.6 to placebo. *Patients with missing HbA1c value at week 26 data were considered non-responders. There were 12.6% of subjects in the XULTOPHY 100/3.6 arm, 12.3% in the insulin degludec arm and 15.5% in the liraglutide arm for whom HbA1c was data missing at week 26. Table 5: 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 combination with metformin. 0.075 U/kg/day. No direct adverse effects on male fertility were observed at dosages up to 1.5 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the human exposure at the MRHD based on plasma AUC comparison. In female Sprague-Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/kg). Multiple imputation modelled “jump-to-control” of the treatment effect for subjects having missing week 26 data. **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 of 0.3% and for superiority of XULTOPHY 100/3.6 to liraglutide. *Estimated using an ANCOVA with treatment, baseline HbA1c, stratum, sub-study, concomitant diabetes treatment and country as factors and baseline response as covariate. Multiple imputation modelled “return to baseline” of the treatment effect for subjects having missing week 26 data. **p<0.001. Primary endpoint was tested for superiority of XULTOPHY 100/3.6 to placebo. *Patients with missing HbA1c value at week 26 data were considered non-responders. There were 12.6% of subjects in the XULTOPHY 100/3.6 arm, 12.3% in the insulin degludec arm and 15.5% in the liraglutide arm for whom HbA1c was data missing at week 26. Table 5: 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 combination with metformin.
were White, 1.2% were Black or African American and 16.2% were Hispanic. 2.6% of patients had eGFR < 60mL/min/1.73m²; none of the patients had eGFR < 30mL/min/1.73m². The mean BMI was 31.2 kg/m².

The starting dose of XULTOPHY® 100/3.6 was 10 units (10 units insulin degludec/0.36 mg liraglutide). The starting dose of insulin glargine U-100 was 10 units. XULTOPHY® 100/3.6 and insulin glargine U-100 were titrated twice weekly to target a fasting blood glucose goal of 72-90 mg/dL. Patients could not increase the dose of XULTOPHY® 100/3.6 and insulin glargine U-100 by more than 4 units per week, and there was no maximum allowed dose of insulin glargine. The patients continued on pre-trial treatment with SGLT2i, with or without other OADs throughout the entire trial. The targeted fasting blood glucose goal was achieved by 49.6% of patients randomized to XULTOPHY® 100/3.6 and 41.9% of patients randomized to insulin glargine at 26 weeks.

At the end of 26 weeks, XULTOPHY® 100/3.6 resulted in a reduction in HbA1c from baseline of 1.97 and insulin glargine U-100 resulted in a reduction of 1.59% (see Table 7). At the end of trial, the average dose of XULTOPHY® 100/3.6 and insulin glargine U-100 was 44 units (44 units insulin degludec/1.58 mg liraglutide). The primary endpoint, change in HbA1c, was tested for superiority of XULTOPHY® 100/3.6 to unchanged liraglutide therapy.

At the end of 26 weeks, there was a reduction in HbA1c from baseline of 1.31% for XULTOPHY® 100/3.6 and 0.36% for liraglutide (see Table 8).

Table 8: Results of a 26-Week Trial with XULTOPHY® 100/3.6 in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Liraglutide up to 1.8 mg Daily

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100/3.6 + metformin + pioglitazone</td>
</tr>
<tr>
<td>Baseline</td>
<td>U-100 + SGLT2i + metformin + pioglitazone</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>9.4</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c &lt; 7%</td>
<td>74%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Baseline</td>
<td>End of Trial (LS Mean)*</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-51</td>
</tr>
</tbody>
</table>

*a Test for superiority evaluated at 5.0% level for significance, (p < 0.0001).

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

1c Diabetes Mellitus Inadequately Controlled on Basal Insulin

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>106</td>
</tr>
<tr>
<td>Baseline</td>
<td>XULTOPHY® 100/3.6 + metformin</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-63.5</td>
</tr>
</tbody>
</table>

*p < 0.01. 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: 44 units insulin degludec/1.66 mg liraglutide). The difference in glycemic lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where insulin degludec dosage can be different than that used in the trial.

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

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>106</td>
</tr>
<tr>
<td>Baseline</td>
<td>XULTOPHY® 100/3.6 + metformin</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-63.5</td>
</tr>
</tbody>
</table>

*p < 0.01. 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: 44 units insulin degludec/1.66 mg liraglutide). The difference in glycemic lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where insulin degludec dosage can be different than that used in the trial.

Table 11: Results of a 26-Week Trial in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>106</td>
</tr>
<tr>
<td>Baseline</td>
<td>XULTOPHY® 100/3.6 + metformin</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-63.5</td>
</tr>
</tbody>
</table>

*p < 0.01. 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: 44 units insulin degludec/1.66 mg liraglutide). The difference in glycemic lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where insulin degludec dosage can be different than that used in the trial.
it is unclear that these observed differences in insulin doses are clinically important. The difference in HbA1c effect observed at 26 weeks may not necessarily reflect the effect in the care setting where insulin glargine may be more rapidly titrated.

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</th>
<th>Insulin glargine U-100 + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>62</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>6.6</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-1.67</td>
</tr>
<tr>
<td>Estimated treatment difference (%CI)</td>
<td>-0.51 [-0.67; -0.34]</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA1c&lt;7%**</td>
<td>68.3%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>161</td>
</tr>
<tr>
<td>Baseline</td>
<td>160</td>
</tr>
<tr>
<td>End of Trial (LS Mean)*</td>
<td>110</td>
</tr>
<tr>
<td>Change from baseline (LS Mean)*</td>
<td>-49.9</td>
</tr>
<tr>
<td>**p&lt;0.01. Primary endpoint was tested for noninferiority of XULTOPHY® 100/3.6 to insulin glargine U-100. The difference in glucose lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where alternative insulin glargine dosage can be used.</td>
<td></td>
</tr>
<tr>
<td>**Estimated using an ANCOVA with treatment and region as fixed factors and baseline response as covariate. Multiple imputation model &quot;returned to baseline&quot; of the treatment effect for subjects having missing week 26 data.</td>
<td></td>
</tr>
<tr>
<td>**Patients with missing HbA1c value at week 26 data were considered non-responders. There were 10.1% of subjects in the XULTOPHY® 100/3.6 arm and 4.7% in the insulin glargine U-100 arm for whom HbA1c data was missing at week 26.</td>
<td></td>
</tr>
</tbody>
</table>

14. Cardiovascular Outcomes Trials in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease Conducted with Liraglutide 1.8 mg and Insulin Degludec

The effect of XULTOPHY® 100/3.6 on the risk of cardiovascular outcomes in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease has not been established. The studies below were conducted with liraglutide 1.8 mg and insulin degludec individually.

VICTOZA® (liraglutide 1.8 mg)

The LEADER trial (NCT01179048) randomized 9340 patients with inadequately controlled type 2 diabetes and cardiovascular disease to liraglutide 1.8 mg or placebo in addition to standard of care treatments for type 2 diabetes for a median follow up of 3.5 years.

Patients either were 50 years of age or older with established, stable cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or chronic heart failure (80% of patients) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (20% of patients). The population was 64% male, 76% Caucasian, 10% Asian, and 8% Black, 12% of the population was Hispanic or Latino. The mean duration of type 2 diabetes was 13 years, the mean HbA1c was 8.7% and the mean BMI was 33 kg/m²; the mean eGFR at baseline was 79 mL/min/1.73 m².

In total, 97.8% of the patients completed the trial; vital status was available for 99.7%. The primary endpoint was the time from randomization to the first occurrence of a major adverse cardiovascular event (MACE) defined: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. No increased risk for MACE was observed with insulin degludec when compared to insulin glargine U-100. The total number of primary MACE endpoints was 681 (325 [8.5%] with insulin degludec and 356 [9.3%] with insulin glargine).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XULTOPHY® 100/3.6 is an injection supplied as a sterile, colorless solution in a 3 mL pre-filled, disposable, single-patient use pen injector. The XULTOPHY® 100/3.6 pen dial is in one unit increment.

Dosage Unit/Strength Package size NDC #
3 mL XULTOPHY® 100/3.6 100 units/mL insulin degludec and 3.6 mg/mL liraglutide Package of 5 0169-2911-15

16.2 Recommended Storage

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 if it has 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 infection, 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 68°F</td>
</tr>
<tr>
<td>(2°C to 8°C)</td>
<td>(15°C to 30°C)</td>
</tr>
<tr>
<td>Until expiration date</td>
<td>Refrigerated</td>
</tr>
<tr>
<td></td>
<td>36°F to 46°F</td>
</tr>
<tr>
<td></td>
<td>(2°C to 8°C)</td>
</tr>
<tr>
<td>21 Days</td>
<td></td>
</tr>
</tbody>
</table>
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 healthcare 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 carcinoma (MTC) 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).

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.

- XULTOPHY® 100/3.6 is not recommended for use in combination with any other product containing liraglutide or another glucagon-like peptide 1 receptor agonist (GLP-1 receptor agonist).

- XULTOPHY® 100/3.6 is not for use in people with type 1 diabetes or people with diabetic ketoacidosis (increased ketones in the blood or urine).

- It is not known if XULTOPHY® 100/3.6 can be used with mealtime insulin.

- It is not known if XULTOPHY® 100/3.6 is safe and effective for use in children.

Who should not use XULTOPHY® 100/3.6? 

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).

- you are choosing an episode of low blood sugar (hypoglycemia).

- you are allergic to insulin degludec, liraglutide or any of the ingredients in XULTOPHY® 100/3.6.

See the end of this Medication Guide for a complete list of ingredients in XULTOPHY® 100/3.6.

What should I tell my healthcare provider before using XULTOPHY® 100/3.6? 

Before using XULTOPHY® 100/3.6, tell your healthcare provider about all your medical conditions, including if you:

- have or have had problems with your pancreas, kidneys, or liver.

- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with XULTOPHY® 100/3.6.

- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.

- are taking certain medicines called GLP-1 receptor agonists.

- have had an allergic reaction to the GLP-1 receptor agonist medicine.

- are pregnant or plan to become pregnant. It is not known if XULTOPHY® 100/3.6 will harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant while using XULTOPHY® 100/3.6.

- are breastfeeding or plan to breastfeed. It is not known if XULTOPHY® 100/3.6 passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using XULTOPHY® 100/3.6.

Tell your healthcare 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 healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

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 healthcare provider tells you to.

- Do not change your dosing schedule without first talking to your healthcare 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 healthcare 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 muscle (intramuscularly) or vein (intravenously) or use in an insulin infusion pump.

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

- If you miss a dose of XULTOPHY® 100/3.6, resume your 1 time daily-dosing schedule at the next scheduled dose. Do not take 2 doses at the same time or increase your dose to make up for the missed dose. If you miss more than 3 days of XULTOPHY® 100/3.6, call your healthcare provider for further instructions about taking XULTOPHY® 100/3.6 at the right dose and to help lower your chance of having an upset stomach.

- Do not dilute XULTOPHY® 100/3.6 with any other liquids.

- Do not mix XULTOPHY® 100/3.6 with any other insulin products or GLP-1 receptor agonists in the same injection.

- Do not split your dose of XULTOPHY® 100/3.6. Give your full dose of XULTOPHY® 100/3.6 in 1 injection.

- 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. Do not take XULTOPHY® 100/3.6 with other GLP-1 receptor agonists. If you take too much XULTOPHY® 100/3.6, call your healthcare provider or go to the nearest hospital emergency room right away.

- Change (rotate) your injection site with each injection to help reduce your chances of getting skin thickening or pits at the injection site. Do not use the same site for each injection.

- Do not share your XULTOPHY® 100/3.6 pen with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your dose of XULTOPHY® 100/3.6 and other diabetes medicines may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

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 healthcare 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 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

- kidney problems (kidney failure). Worsening of kidney failure and sudden kidney failure have happened in people with kidney problems and in people without kidney problems, who have taken liraglutide, one of the ingredients in XULTOPHY® 100/3.6. Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. Tell your healthcare provider if you have diarrhea, nausea, or vomiting. Drink plenty of fluids to help reduce your risk of dehydration during treatment with XULTOPHY® 100/3.6.

- serious allergic reactions. Stop using XULTOPHY® 100/3.6 and get medical help right away if you have any symptoms of a serious allergic reaction including:

- hives

- rash

- itching

- fast heartbeat

- fainting or feeling dizzy

- gallbladder problems. Gallbladder problems have happened in some people who take liraglutide, an ingredient in XULTOPHY® 100/3.6. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:

- pain in the right or middle upper stomach area

- nausea and vomiting

- your skin or the white part of your eyes turn yellow

- fever

- low potassium in your blood (hypokalemia). 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 or heart problems before. If you already have heart failure, it may get worse while you take TZDs with XULTOPHY® 100/3.6. Your healthcare provider should monitor you closely while you are taking TZDs with XULTOPHY® 100/3.6. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, tiredness, swelling of your ankles or feet, and sudden weight gain. Treatment with TZDs and XULTOPHY® 100/3.6 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.
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 A/S DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 02/2019
Instructions for Use

**XULTOPHY® 100/3.6 (ZUL-to-fye)**

**INSULIN 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 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 new NovoFine® or NovoTwist® needle
- **alcohol swab**
- a sharps container for throwing away used pens and needles. See “After your injection” at the end of these instructions.

**Preparing 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.
- **Do not use XULTOPHY® 100/3.6 if it is 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**

- Pen scale
- Window
- Dose counter
- Dose selector
- Pen cap
- Dose button
- Priming symbol

**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.
- Pull pen cap straight off 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 dosing schedule without first talking to your healthcare provider.
- **Turn the dose selector to select the dose you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The odd numbers are printed on the dial.
  - The even numbers are shown as lines.

- **The XULTOPHY® 100/3.6 pen scale will show you how much XULTOPHY® 100/3.6 is left in your pen** (See Figure L).
  - 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 that is left in your pen. 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.

---

Examples

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

---

(XFigure A)

(XFigure B)

(XFigure C)

(XFigure D)

(XFigure E)

(XFigure F)

(XFigure G)

(XFigure H)

(XFigure I)

(XFigure J)

(XFigure K)

(XFigure L)
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. Do not use the same injection site for each injection.

Step 11:

Choose your injection site and wipe the skin with an alcohol swab (See Figure O). 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.

Note: If you do not have a sharps container, follow the steps below:

- Carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
- 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.

Step 17:

- Replace the pen cap by pushing it straight on (See Figure T).

After your injection:

- Put your used XULTOPHY® 100/3.6 pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and pens 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
  - upright and stable during use
  - 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 38°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.

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

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For more information call Novo Nordisk at 1-800-727-6500
Revised: 08/2019
For additional information about Xultophy® 100/3.6 go to: www.Xultophy10036.com
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