HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XULTOPHY® 100/3.6 safely and effectively. See full prescribing information for XULTOPHY® 100/3.6. XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection), for subcutaneous use
Initial U.S. Approval: 2016
WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.
• Liraglutide, one of the components of XULTOPHY® 100/3.6, causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY® 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been established (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 Usage (1) 02/2019
Dosage and Administration (2.2) 02/2019
Dosage and Administration (2.5) 11/2019
Contraindications (4) 02/2019
Warnings and Precautions (5.2, 5.8, 5.9) 02/2019
Warnings and Precautions (5.4) 11/2019

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:
• 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 (10 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once-daily (2.2).
• Administer once daily at same time each day with or without food (2.2).
• Inject XULTOPHY® 100/3.6 subcutaneously into the thigh, upper arm, or abdomen (2.5).
• Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis (2.5).
• 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).

DOSE 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 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).
• Hypersensitivity to any component of XULTOPHY® 100/3.6 (5.1).

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 1-800-727-6508 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

USE IN SPECIFIC POPULATIONS
Pregnancy: XULTOPHY® 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS
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Xultophy® 100/3.6 (insulin degludec and liraglutide injection)

FULL PRESCRIBING INFORMATION

1 INDICTIONS 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 adequate glycemic control on diet alone.

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

• XULTOPHY® 100/3.6 is not recommended 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 Precautions (5.2)).

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) 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 0.56 mg of liraglutide) 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 Contraindications (4), Warnings and Precautions (5.1)).

• Train patients on proper use and injection technique before initiating XULTOPHY® 100/3.6.

• During changes to a patient’s insulin regimen, increase the dose to make up for the missed dose.

• Always check the label on the XULTOPHY® 100/3.6 pen before administration. Only use XULTOPHY® 100/3.6 if the solution appears clear and colorless.

• 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)).

• The XULTOPHY® 100/3.6 subcutaneously into the thigh, upper arm, or abdomen.

• 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 dilute or mix XULTOPHY® 100/3.6 intravenously, intramuscularly, or in an insulin infusion pump.

• Do not divide 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 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 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 (5.4)).

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 rodents (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice. (see Nonclinical Toxicology (13)). Malignant thyroid C-cell carcinomas were detected in 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 is insuffi-
client to establish or exclude a causal relationship between MTC and liraglutide use in humans.

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. These 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)]. 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 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.

5.9 Acute Gallbladder Disease

A cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)] showed that XULTOPHY 100/3.6 is contraindicated in patients who have had hypersensitivity reactions to insulin degludec, liraglutide or one of the excipients of these products. XULTOPHY 100/3.6 is contraindicated in patients using insulin-containing products, 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 dose reduction 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 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 2.6% were older than 75 years; 52.0% were male, 75.0% were white, 8.2% were Black or African American and 15.9% were Hispanic or Latino. The mean body mass index (BMI) was 31.8 kg/m². 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 m² and 6.24% 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
Xultophy® 100/3.6 (insulin degludec and liraglutide injection)

| Table 4: Hypoglycemia Episodes Reported in XULTOPHY® 100/3.6-Treated Patients with T2DM |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| XULTOPHY® 100/3.6               | XULTOPHY® 100/3.6 | XULTOPHY® 100/3.6 | XULTOPHY® 100/3.6 | XULTOPHY® 100/3.6 | XULTOPHY® 100/3.6 | XULTOPHY® 100/3.6 |
| NCT01336023                  | NCT01619162        | NCT02723368         | NCT01675116        | NCT01952573        | NCT01952145         |
| Total Subjects (N)            | 825               | 288               | 209               | 291               | 199               | 278               |
| Severe Hypoglycemia (%)       | 0.2               | 0.7               | 0.5               | 0.3               | 0.5               | 0.0               |
| Hypoglycemia with a glucose level below 54 mg/dL (%) | 27.6               | 37.2               | 14.4               | 27.1               | 22.1               | 24.8               |

*episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, eructation, gastroesophageal reflux disease, abdominal distention and decreased appetite 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 of observation). Most of these 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. The incidence of cholecystitis was 0.2% in both liraglutide-treated and placebo-treated patients. In a cardiovascular outcomes trial (LEADER trial) [see Clinical Studies (14.4)], the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in liraglutide-treated 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.

Initiation of insulin containing products and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transient, reversible opthalmologic retinopathy, 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 lipohypertrophy (thickening of adipose tissue) and lipatrophy (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, 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.

6.2 Immuneogenicity

**XULTOPHY® 100/3.6**

As with all therapeutic proteins, there is potential for immuneogenicity. 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, a 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.

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 require the adjustment of any dose of XULTOPHY® 100/3.6 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, 30.8% 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 antibodies against liraglutide. 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 incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies of other products.

Approximately 50%-70% of liraglutide-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of such antibodies. The majority of antibody positive patients had low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies detected in 8.6% of these 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 the presence of such antibodies may not directly affect the clinical benefit provided by XULTOPHY® 100/3.6. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these 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. 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.

In five double-blind glycemic control trials of liraglutide, events from a composite of adverse events potentially related to immunogenicity (e.g. urticaria, angioedema) occurred among 0.8% of liraglutide-treated patients and among 0.4% of comparator-treated patients. Urticaria was reported in 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 against native GLP-1. Across clinical studies, 0.4% developed cross-reacting antibodies against native GLP-1.

**TRESIBA® (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 during the study. In these trials, between 96.7% and 99.7% of patients who were positive for anti-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.

**Insulin degludec (one of the components of XULTOPHY® 100/3.6)**

Localized cutaneous amyloidosis at the injection site has occurred. Hypoglycemia has been reported with repeated insulin injections.
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.
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.
- Hepatobiliary disorders: elevations of liver enzymes, hyperbilirubinemia, cholestasis, 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 possibly close monitoring [see Dosage and Administration (2.2); Warnings and Precautions (5.6)].

Drugs That May Increase the Risk of Hypoglycemia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fribates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramilide, salicylates, somatostatin analogs (e.g., octrreotide), and sulfonamide antibiotics</td>
<td>Dose reductions and increased frequency of glucose monitoring may be required when Xultophy® 100/3.6 is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics (e.g., olanzapine and quetiapine), selective serotonin reuptake inhibitors, somatostatin analogues (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones</td>
<td>Dose increases and increased frequency of glucose monitoring may be required when Xultophy® 100/3.6 is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

Drugs That May Increase the Risk of Hypoglycemia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol, beta-blockers, clenbuterol, and lithium salts</td>
<td>Dose increases and increased frequency of glucose monitoring may be required when Xultophy® 100/3.6 is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, clenbuterol, quinagolide, and reserpine</td>
<td>Increased frequency of glucose monitoring may be required when Xultophy® 100/3.6 is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

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 may be risks 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 pregnancy [see Clinical Considerations].

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 exposure at the maximum recommended human dose (MRHD) of 1.8 mg/kg/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 of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20–25% in 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 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 studied in investigations covering fertility, embryofetal 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 of 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 during gestation day 2 to day 20 showed signs of maternal toxicity, including embryofetal death and delayed delivery. However, a dose of 0.75 mg/kg/day, reflecting the human exposure at the MRHD based on plasma AUC comparison, did not 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.

8.2 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 along with the mother’s clinical need for Xultophy® 100/3.6 and any potential adverse effects on the breastfed infant from Xultophy® 100/3.6 or from the underlying maternal condition.

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.

8.3 Pediatric Use

Safety and effectiveness of Xultophy® 100/3.6 have not been established in pediatric patients.

8.4 Geriatric Use

Of the total number of 1881 subjects in clinical studies of Xultophy® 100/3.6, 375 (19.9%) were 65 years and over, while 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 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 older patients.

8.5 Renal Impairment

There is limited experience with Xultophy® 100/3.6 in patients with mild and moderate 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 clinical study that included patients with moderate renal 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 (14.4), 1932 (41.4%) 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 and worsening of chronic renal failure, which may sometimes require hemodialysis [see Warnings and Precautions (5.7) and Adverse Reactions (6.2)].

8.6 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 moderate hepatic impairment, 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)].

8.7 Gastropareisis

Liraglutide, one of the components of Xultophy® 100/3.6, slows gastric emptying. Xultophy® 100/3.6 has not been studied in...
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 (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the molecule. The molecular formula of insulin degludec is C17H30NO5751.2 Daltons. The structural formula (Figure 2) is:

Figure 2: 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 spacer on the remaining lysine residue at position 26. The molecular formula of liraglutide is C17H30NO5751.2 Daltons and the molecular weight is 3751.2 Daltons. The structural formula (Figure 2) is:

Figure 2: Structural Formula of Liraglutide

Xultophy® 100/3.6 (insulin degludec and liraglutide injection) is a combination of a long-acting basal human insulin analog, insulin degludec, and a GLP-1 receptor agonist, liraglutide. Insulin degludec and liraglutide are extensively bound to plasma proteins. Steady state concentrations of insulin degludec and liraglutide were achieved after 2-3 days of daily administration.

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 1131 h•mg/mL and of liraglutide 1227 h•ng/mL based on population pharmacokinetic analysis. The corresponding maximum concentrations were 5196 pmol/L for insulin degludec and 55 ng/mL for liraglutide. Steady state concentrations of insulin degludec and liraglutide are reached after 2-3 days of daily administration.

Distribution
In vivo 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 oral medicinal products. Interaction 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 reach the maximum dose of 1.8 mg/day. 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.

Diozepin
A single dose of diozepin 1 mg was administered 7 hours after the dose of liraglutide at steady state. The concomitant administration with liraglutide 1.8 mg/day increased AUC of diozepin by 15%; Cmax decreased by 31%. Diozepin median time to maximal concentration (Tmax) was delayed from 1 h to 1.5 h.

Lisinopril
A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide at steady state. The co-administration with liraglutide resulted in a reduction of lisinopril AUC by 15%; Cmax decreased by 26%. Lisinopril median Tmax was delayed from 6 h to 8 h with liraglutide.

Atorvastatin
Liraglutide did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide at steady state. Atorvastatin Cmax was decreased by 38% and median Tmax was delayed from 1 to 3 hours over the course.

Acetaminophen
Liraglutide did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of liraglutide at steady state. Acetaminophen Cmax was decreased by 31% and median Tmax 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 Cmax increased by 37% and median Tmax did not 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 Cmax by 12% and 18%, respectively, and there was no effect of liraglutide on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel AUC by 18%. Liraglutide delayed Tmax 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 carcinogenesis, mutagenesis 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 a comparator, Sprague Dawley rats were dosed subcutaneously with insulin degludec at 3.6, 7.2, and 14.7 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/day. No treatment-related increases in incidences of hyperplasia, benign or malignant tumors were recorded in female mammary gland glands 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 hyperplastic or neoplastic lesions were seen 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 exposure at the MRHD) did not show any 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 liraglutide administered subcutaneously once daily for 52 weeks. In this study, there were rare findings during carcinogenicity testing in rats.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

A total of 3908 patients with type 2 diabetes participated in 6 randomized, parallel and active or placebo-controlled phase 3 trials of 26 weeks duration.

Three studies were conducted in patients inadequately controlled on one or more OADs (e.g. metformin, pioglitazone, sulfonylurea, or basal insulin) (Table 5).

Three studies were conducted in patients converting from insulin glargine to basal insulin: one study was conducted in patients converting from liraglutide with (doses up to 1.8 mg) (Table 8), one study was conducted in patients converting from basal insulin (between Table 9, and one study was conducted in patients converting from insulin glargine U-100 (Table 10).

In all trials, XULTOPHY 100/3.6 was titrated twice weekly by increments or decrements of 2 units (2 insulin degludec units/0.072 mg liraglutide), towards a pre-specified fasting blood glucose target, with the same titration algorithm used for basal insulin comparators.

14.2 Patients with Type 2 Diabetes Uncontrolled on OAD Treatment

NCT01336023: The efficacy and safety of XULTOPHY® 100/3.6 compared to placebo were studied in a 26-week, randomised, double-blind, treat-to-target trial in 435 patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or in combination with metformin.

The mean age of the trial population was 59.8 years, and mean duration of diabetes was 9.1 years, 52% were male, 75.4% were White, 6.7% were Black or African American and 9.2% were Hispanic. 10.6% had an eGFR < 60mL/min/1.73m²; no patients had an eGFR < 30mL/min/1.73m². The mean BMI was 31.5 kg/m².

XULTOPHY® 100/3.6 was started at 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-trial treatment with sulfonylurea, with or without metformin throughout the trial.

XULTOPHY 100/3.6 for 26 weeks resulted in a statistically significant reduction in mean HbA₁c compared to placebo (see Table 6).

The end of trial dose of XULTOPHY® 100/3.6 was 28 units (28 units insulin degludec/1.01 mg liraglutide).

XULTOPHY® 100/3.6 + sulfonylurea + metformin

Percent change from baseline HbA₁c compared to placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA₁c (%)</th>
<th>Baseline</th>
<th>N of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.8</td>
<td>7.8</td>
<td>28</td>
</tr>
<tr>
<td>XULTOPHY® 100/3.6</td>
<td>-0.59</td>
<td>7.24</td>
<td>38</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 Sulfonylurea Alone or in Combination with Metformin
twice weekly to target a fasting blood glucose goal of 72-90 mg/dL. The end of trial dose of XULTOPHY 100/3.6 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 compared to insulin glargine U-100 at baseline (Table 8).

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 insulin glargine (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 Lisprodilate or DPP4 Inhibitor

<table>
<thead>
<tr>
<th>Total (N)</th>
<th>HbA1c (%)</th>
<th>XULTOPHY 100/3.6</th>
<th>Insulin Glargine</th>
<th>Change from baseline</th>
<th>Estimated treatment difference [95% CI]</th>
<th>Percentage of patients achieving HbA1c &lt;7%</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>232</td>
<td>7.8</td>
<td>-1.31</td>
<td>-0.36</td>
<td>-0.95 [-1.15; -0.75]</td>
<td>47.6%</td>
<td>30.2%</td>
<td>116</td>
</tr>
<tr>
<td>End of Trial (LS Mean)</td>
<td>6.4</td>
<td>112</td>
<td>153</td>
<td>-11.0</td>
<td>-51.1</td>
<td>22.6%</td>
<td>57.3</td>
</tr>
</tbody>
</table>

The targeted fasting blood glucose goal was achieved in 24.0% of patients in the XULTOPHY 100/3.6 arm and 19.0% in the insulin glargine arm for whom HbA1c was missing at week 26.

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

* Test for superiority evaluated at 5.0% level for significance. (p<0.0001)
* Estimated using an ANCOVA with treatment, pre-trial liraglutide therapy and region as fixed factors and baseline response as covariate. Multiple imputation modelled "return to baseline" of the treatment effect for subjects having missing week 26 data.
* 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 and 13.1% in the insulin glargine 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>Total (N)</th>
<th>XULTOPHY 100/3.6</th>
<th>Insulin glargine</th>
<th>Change from baseline</th>
<th>Estimated treatment difference [95% CI]</th>
<th>Percentage of patients achieving HbA1c &lt;7%</th>
<th>FPG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>7.8</td>
<td>6.9</td>
<td>-1.94</td>
<td>-0.89 [-1.10; -0.68]</td>
<td>57.3%</td>
<td>22.6%</td>
</tr>
<tr>
<td>End of Trial (LS Mean)</td>
<td>6.9</td>
<td>7.7</td>
<td>110</td>
<td>-1.05</td>
<td>-63.5</td>
<td>55.5</td>
</tr>
</tbody>
</table>

The mean dose of insulin glargine U-100 in patients entering the trial was 32 units.

**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 glargine arm for whom HbA1c data was missing at week 26.

The efficacy and safety of XULTOPHY 100/3.6 compared to insulin glargine U-100, both once daily and added on to metformin, were studied in a 26-week randomized, open-label, two-arm parallel trial in 557 patients with type 2 diabetes mellitus inadequately controlled on insulin glargine U-100 and metformin.

The mean age of the trial population was 58.8 years and mean duration of diabetes was 11.5 years. 50.3% were male. 94.6% were White, 2% Black or African American. 43.1% were Hispanic. 6.3% were of Asian or Pacific Island heritage. 2% were of other or unknown heritage. 6.3% of patients had eGFR < 60mL/min/1.73m, one patient had eGFR < 30mL/min/1.73m. The mean BMI was 31.7 kg/m². The mean dose of insulin glargine U-100 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 care setting where alternative insulin degludec dosage can be used.

Maximum dose 50 units
* Estimated using an ANCOVA with treatment, country, and previous antidiabetic treatment as fixed factors and baseline response as covariate. Multiple imputation modelled "return to control" of the treatment effect for subjects having missing week 26 data.

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 glargine arm for whom HbA1c data was missing at week 26.

**Table 8:** XULTOPHY 100/3.6 in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Lisprodilate

**Table 9:** XULTOPHY 100/3.6 in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin
100/3.6 pen dials in one unit

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

Package size NDC #  
Package of 5 0169-2911-15

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 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>
<th>Until expiration date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>38°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>
<td>(2°C to 8°C)</td>
</tr>
</tbody>
</table>

Date of Issue: 11/2019
Version: 5
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Manufactured by: Novo Nordisk A/S  
DK-2880 Bagsvaerd, Denmark  
For information about XULTOPHY® 100/3.6 contact: Novo Nordisk Inc. 800 Scudders Mill Road Plainsboro, NJ 08536 1-800-727-6500

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US19XUM00237 12/2019

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 (5.6)].

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

Inform female patients of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

14.4 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, 78% Caucasian, 10% Asian, and 9% 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 33.6 kg/m²; the mean eGFR was at baseline was 79 mL/min/1.73 m². In total, 96.8% 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 as: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. No increased risk for MACE was observed with liraglutide 1.8 mg. The total number of primary component MACE endpoints was 1302 (908[13.0%] with liraglutide 1.8 mg and 694 (14.9%) with placebo).

TRESIBA® (insulin degludec)

The DEVOTE trial (NCT01959529) randomized 7637 patients with inadequately controlled type 2 diabetes and cardiovascular disease to either insulin degludec or insulin glargine U-100. Each was administered once-daily in addition to standard of care treatments for diabetes for a median duration of follow up of 2 years. Patients either were 50 years of age or older and had established, stable cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or chronic heart failure (65% of patients) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of patients). The population was 63% male, 76% White 11% Black or African American, and 10% Asian; 15% of the population was Hispanic or Latino. The mean HbA1c was 8.4% and the mean BMI was 33.6 kg/m². The baseline mean eGFR was 60 mL/min/1.73 m². In total, 98% of the patients completed the trial; vital status was known at the end of the trial for 99%. The primary endpoint was the time from randomization to the first occurrence of a major adverse cardiovascular event (MACE), defined as: 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).

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>Dosage Unit/Strength</th>
<th>Package size NDC #</th>
<th>100/3.6 Pen Between Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mL single-patient use XULTOPHY® 100/3.6 pen (100 units/mL insulin degludec and 3.6 mg/mL liraglutide)</td>
<td>Package of 5 0169-2911-15</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Prior to first use</th>
<th>After first use</th>
<th>Until expiration date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>38°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>
<td>(2°C to 8°C)</td>
</tr>
</tbody>
</table>
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 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.

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 having an episode of low blood sugar (hypoglycemia).
  - you are allergic to insulin degludec, liraglutide or any of the ingredients in 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 a 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.

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 is the most important information I should know about XULTOPHY 100/3.6?  
- 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 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  
- blurred vision  
- anxiety, irritability, or mood changes  
- slurred speech  
- confusion or drowsiness  
- weakness  
- fast heartbeat  
- feeling jittery  
- 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  
  - swelling of your face, lips, tongue, or throat  
  - problems breathing or swallowing  
  - sudden coughing  
  - chest pain or tightness  
- 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 turns yellow  
- 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 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: 11/2019
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”) 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 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.
- 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.

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

Step 4: Prime your XULTOPHY® 100/3.6 pen:
- Pull off the inner needle cap and throw it away (See Figure F).
- Pull off the outer needle cap. Do not throw it away (See Figure F).
- Select a new NovoFine® or NovoTwist® needle.

Step 5: Set the dose counter.
- Turn the dose selector until it stops. The dose counter will line up with the dose button.
- The XULTOPHY® 100/3.6 pen scale will show you how much XULTOPHY® 100/3.6 is left in your pen (See Figure I).

Step 6: 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 button.
- The XULTOPHY® 100/3.6 pen scale will show you how much XULTOPHY® 100/3.6 is left in your pen (See Figure I).

Step 7: 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).

Example Approx. 200 units left

27 units selected

16 units selected

Examples

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.

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 even numbers are printed on the dial.
- The odd 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 I).

- 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 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.

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.

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: 11/2019
For additional information about Xultophy&reg; 100/3.6 go to: www.Xultophy10036.com

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