PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

XULTOPHY®

insulin degludec + liraglutide injection

100 units/mL + 3.6 mg/mL

Solution for injection in a pre-filled pen

Subcutaneous use

House Standard

Antidiabetic agent

Novo Nordisk Canada Inc.
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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Xultophy® is a combination of insulin degludec and liraglutide and is indicated for once-daily treatment, as an adjunct to diet and exercise and in combination with oral medicinal products for the treatment of diabetes (see CLINICAL TRIALS for patient populations and drug combinations tested), to improve glycemic control in adults with type 2 diabetes mellitus.

Xultophy® should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Patients on basal insulin or GLP-1 receptor agonist should not continue these drugs when beginning treatment with Xultophy®, since Xultophy® contains both basal insulin and a GLP-1 receptor agonist.

Xultophy® has not been studied in combination with prandial insulin (short acting).

1.1 Pediatrics

Pediatrics (< 18 years of age): Xultophy® is not indicated for use in children and adolescents below 18 years of age. No studies have been performed with Xultophy® in patients below 18 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): Xultophy® can be used in elderly patients. No overall difference in safety or efficacy was observed in clinical trial subjects ≥65 years of age compared to younger patients, but greater sensitivity of older individuals cannot be ruled out. Xultophy® was studied in a limited number of patients 75 years of age or older (see WARNINGS AND PRECAUTIONS, Special Populations; DOSAGE AND ADMINISTRATION; and ACTION AND CLINICAL PHARMACOLOGY sections). Glucose monitoring is to be intensified and the dose adjusted on an individual basis.

2 CONTRAINDICATIONS

Insulin degludec and liraglutide injection is contraindicated in patients who are hypersensitive to Xultophy®, insulin degludec, liraglutide (the mono-components of Xultophy®), or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Pregnant or breastfeeding women.
- During episodes of hypoglycemia (see OVERDOSAGE).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hypoglycemia is the most common adverse effect of insulin products. As with all insulin products the timing of hypoglycemia may differ. Glucose monitoring shall be performed for all patients with Diabetes Mellitus treated with insulins (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia).

- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma or even death.
- Any transfer of insulin products should be made cautiously and only under medical supervision (see DOSAGE AND ADMINISTRATION).
- **Xultophy®** should be inspected visually prior to administration and should only be used if the solution appears clear and colourless.
- **Xultophy®** must not be mixed with any other insulin.
- **Xultophy®** is a long-acting insulin-containing product and MUST NOT be administered Intravenously (IV) or be used in insulin infusion pumps.

Risk of Thyroid C-cell Tumours

- Liraglutide, one of the components of Xultophy® causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.
- Liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Patients should be counselled regarding the risk and symptoms of thyroid tumours.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Xultophy® is given once daily by subcutaneous administration.
- Xultophy® can be added to combined metformin and sulfonylurea therapy. The current dose of sulfonylurea can be lowered at the discretion of the doctor to minimize the risk of unacceptable hypoglycemia.
- Xultophy® is not recommended as first-line treatment for patients inadequately controlled on diet and exercise.
- Xultophy® can be administered at any time of the day independent of meals, preferably at the same time of the day.
- Xultophy® is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycemic control via dose adjustment based on fasting plasma glucose.
- As with all insulin products, adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

4.2 Recommended Dose and Dosage Adjustment

The following are important dosing information for Xultophy®, a combination of insulin degludec and liraglutide:

- Discontinue therapy with GLP-1 receptor agonist or basal insulin prior to initiation of Xultophy®
- The recommended starting dose of Xultophy® 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.
- The recommended starting dosage of Xultophy® in patients currently on basal insulin or GLP-1 receptor agonist is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily.
- The maximum daily dosage of Xultophy® is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide).
- The Xultophy® pen delivers doses from 1 to 50 units with each injection (see Table 1)

Table 1 presents the units of insulin degludec and the milligrams of liraglutide in each dosage of Xultophy®

Table 1 : Units of Insulin Degludec and Milligrams of Liraglutide in Each Dosage of Xultophy®

Xultophy® (dose counter display)*	insulin degludec component dose	liraglutide component dose	Comment
0	0	0	
1	1 unit	0.04 mg	
2	2 units	0.07 mg	
3	3 units	0.11 mg	
4	4 units	0.14 mg	
5	5 units	0.18 mg	
6	6 units	0.22 mg	
7	7 units	0.25 mg	
8	8 units	0.29 mg	
9	9 units	0.32 mg	
10	10 units	0.36 mg	**Recommended starting dose for patients naïve to basal insulin or GLP-1 receptor agonist**
11	11 units	0.4 mg	
12	12 units	0.43 mg	
13	13 units	0.47 mg	
14	14 units	0.5 mg	
15	15 units	0.54 mg	
16	**16 units**	**0.58 mg**	**Recommended starting dose for patients currently on basal insulin or GLP-1 receptor agonist**
17	17 units	0.61 mg	
18	18 units	0.65 mg	
19	19 units	0.68 mg	
20	20 units	0.72 mg	
21	21 units	0.76 mg	
22	22 units	0.79 mg	
23	23 units	0.83 mg	
24	24 units	0.86 mg	

Xultophy® (dose counter display)*	insulin degludec component dose	liraglutide component dose	Comment
25	25 units	0.90 mg	
26	26 units	0.94 mg	
27	27 units	0.97 mg	
28	28 units	1.01 mg	
29	29 units	1.04 mg	
30	30 units	1.08 mg	
31	31 units	1.12 mg	
32	32 units	1.15 mg	
33	33 units	1.19 mg	
34	34 units	1.22 mg	
35	35 units	1.26 mg	
36	36 units	1.30 mg	
37	37 units	1.33 mg	
38	38 units	1.37 mg	
39	39 units	1.40 mg	
40	40 units	1.44 mg	
41	41 units	1.48 mg	
42	42 units	1.51 mg	
43	43 units	1.55 mg	
44	44 units	1.58 mg	
45	45 units	1.62 mg	
46	46 units	1.66 mg	
47	47 units	1.69 mg	
48	48 units	1.73 mg	
49	49 units	1.76 mg	
50	**50 units**	**1.8 mg**	**Maximum daily dosage** (see WARNINGS AND PRECAUTIONS)

* The dose counter on the Xultophy® pen displays numbers for the even units and displays lines for the odd units.

Titration of Xultophy®

- After starting the recommended starting dose of Xultophy®, 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. The dosage of Xultophy® is between 10 to 50 units (see Table 1).
- To minimize the risk of hypoglycemia or hyperglycemia, additional titration may be needed with changes in physical activity, meal patterns (i.e., macronutrient content or timing of food intake), or renal or hepatic function; during acute illness; or when used with other medications (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- The dosage of Xultophy® should be individualized and titrated under the supervision of a health care provider in accordance with the metabolic needs of the patient and the glycemic control target and with appropriate glucose monitoring.

Table 2: Recommended Titration of Xultophy® (Once or Twice Weekly)[1]

Self-Monitored Fasting Plasma Glucose	Xultophy® Dosage Adjustment
Above target range	+ 2 units
Within target range	0 units
Below target range	- 2 units

[1] The recommended Xultophy® dosage is between 10 to 50 units (see Table 1)

Renal impairment
When Xultophy® is used in patients with mild or moderate renal impairment, glucose monitoring is to be intensified and the dose adjusted on an individual basis. Xultophy® cannot be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Hepatic impairment
When Xultophy® is used in patients with hepatic impairment, glucose monitoring is to be intensified and the dose adjusted on an individual basis.

Xultophy® has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides or prandial insulin.

Pediatrics
Health Canada has not authorized an indication for pediatric use.

4.3 Administration

- The Xultophy® pen is for single-patient-use only (see WARNINGS AND PRECAUTIONS).
- Train patients on proper use and injection technique before initiating Xultophy®.
- Always check the label on the Xultophy® pen before administration (see WARNINGS AND PRECAUTIONS).
- Inspect visually for particulate matter and discoloration prior to administration. Only use Xultophy® if the solution appears clear and colorless.
- Inject Xultophy® subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).
- Use Xultophy® with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
- The Xultophy® pen dials in one-unit increments.
- Do not administer Xultophy® intravenously, intramuscularly, or in an insulin infusion pump.
- Do not dilute or mix Xultophy® with any other insulin products or solutions.
- Do not split the dose of Xultophy®.

4.4 Missed Dose

- Instruct patients who miss a dose of Xultophy® 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® dose, reinitiate Xultophy® at the recommended starting dose to mitigate any gastrointestinal symptoms associated with reinitiation of treatment (see DOSAGE AND ADMINISTRATION).

5 OVERDOSAGE

Limited data are available with regard to overdose of Xultophy®.

Hypoglycemia may develop if a patient is dosed with more Xultophy® than required:

- Mild hypoglycemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries sugar-containing products
- Severe hypoglycemic episodes, where the patient is not able to treat himself, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous use	Injectable, 100 units/mL (insulin degludec) + 3.6 mg/mL (liraglutide)	Glycerol, hydrochloric acid, phenol, sodium hydroxide, water for injections and zinc acetate.

Xultophy® is an injection supplied as a sterile, clear, colorless solution in a 3 mL pre-filled, disposable, single-patient use pen injector.

Pack sizes of 3 and 5 pre-filled pens.

Not all pack sizes may be marketed.

Xultophy® pre-filled pens are recommended to be used with NovoFine®, and NovoTwist® needles

7 DESCRIPTION

Xultophy® (insulin degludec and liraglutide injection), for subcutaneous use, is a fixed-ratio combination of a long-acting basal human insulin analog, insulin degludec, and a GLP-1 receptor agonist, liraglutide. Consult the Product Monographs for Tresiba® and Victoza® for further information about the component drugs.

Xultophy® is a sterile, aqueous, clear, and colorless solution. Each pre-filled pen contains 3 mL equivalent to 300 units of insulin degludec and 10.8 mg of liraglutide. Each mL contains 100 units of insulin degludec and 3.6 mg of liraglutide. One unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide.

8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Xultophy® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulins therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhea) (See ADVERSE REACTIONS). Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph, (see WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin-containing product, including Xultophy®, is contemplated.

The Xultophy® pen should never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Avoidance of medication errors

Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between Xultophy® and other injectable diabetes medicinal products

Carcinogenesis and Mutagenesis

Risk of Thyroid C-Cell Tumours:

Liraglutide, one of the components of Xultophy®, causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice (see NON-CLINICAL TOXICOLOGY). Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether liraglutide 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 could not be confirmed by clinical or nonclinical studies. Cases of thyroid C-cell hyperplasia have been reported in liraglutide clinical trials. The data are insufficient to establish or exclude a causal relationship between thyroid C-cell tumors and liraglutide in humans.

Counsel patients regarding the risk of MTC and the symptoms of thyroid tumours (e.g. a mass in the neck, dysphagia, dyspnea or persistent hoarseness).

Liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. The clinical value of routine monitoring of serum calcitonin has not been established.

Cardiovascular
There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and Xultophy® should therefore be used with caution in these patients. There is no experience in patients with congestive heart failure NYHA class III-IV and Xultophy® is therefore not recommended in these patients.

Increase in Heart Rate:
A 24 h time-averaged increase in mean heart rate of 7-8 bpm was reported with liraglutide treatment in a clinical trial in healthy volunteers undergoing serial ECG monitoring. In patients with diabetes, including patients with established and high risk for CV disease in the LEADER trial, a mean increase in heart rate from baseline of 2 to 4 beats per minute was observed with liraglutide in long-term clinical trials. The incidence of a composite endpoint for all tachyarrhythmia in pooled liraglutide Phase 3a clinical trials in diabetic patients was higher for liraglutide than for placebo.

PR Interval Prolongation:
A prolongation of the mean PR interval of up to 10 ms was reported with liraglutide treatment in a clinical trial in healthy volunteers. In healthy volunteers and in patients with diabetes, the incidence of first degree atrioventricular (AV) block was higher with liraglutide than with placebo. The clinical significance of these changes is not fully known; however, because of limited clinical experience in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) and heart rhythm disturbances (e.g., tachyarrhythmia), caution should be observed in these patients.

Driving and Operating Machinery
Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism
Hypoglycemia
Hypoglycemia is the most common adverse reaction of all insulin preparations. 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®, or any insulin, should not be used during episodes of hypoglycemia (see CONTRAINDICATIONS).

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, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) (see DRUG INTERACTIONS), or in patients who experience recurrent hypoglycemia.

<u>Risk Factors for Hypoglycemia</u>
The timing of hypoglycemia usually reflects the duration of action of the administered insulin formulation and, in general, is highest when the glucose-lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of Xultophy®

may vary among different individuals or at different times in the same individual and depends on many conditions, including both the blood supply and temperature at the injection site.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication (see DRUG INTERACTIONS). Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

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

Hypoglycemia Due to Medication Errors
Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between Xultophy® and other injectable diabetes medicinal products.

Do not transfer Xultophy® from the Xultophy® pen to a syringe. The markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia.

Hypoglycemia Due to Changes in Insulin Regimen
Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed (see DOSAGE AND ADMINISTRATION).

When Xultophy® is used in combination with sulphonylurea, the risk of hypoglycemia may be lowered by a reduction in the dose of sulphonylurea. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes of the Xultophy® dose. Patients whose blood-glucose control is greatly improved (e.g. by intensified therapy) may experience a change in their usual warning symptoms (see ADVERSE REACTIONS, Hypoglycemia) of hypoglycemia, and must be advised accordingly. Usual warning symptoms of hypoglycemia may disappear in patients with long-standing diabetes. As with all products with a basal insulin component, prolonged effect of Xultophy® may delay recovery from hypoglycemia.

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients must be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

Hyperglycemia
Inadequate dosing and/or discontinuation of anti-diabetic treatment may lead to hyperglycemia

and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycemia and thereby cause an increased requirement for anti-diabetic treatment.

Usually, the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. Administration of rapid-acting insulin should be considered in situations of severe hyperglycemia. Untreated hyperglycemic events eventually lead to hyperosmolar coma/diabetic ketoacidosis, which is potentially lethal.

In case of discontinuation of Xultophy®, ensure that instruction for initiation of alternative anti-diabetic medication is followed.

Thyroid Disease
Thyroid adverse events, such as goitre, have been reported in clinical trials, in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in these patients.

Gastrointestinal
Gastrointestinal Disease
The use of liraglutide is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhea.

There is no experience with Xultophy® in patients with inflammatory bowel disease and diabetic gastroparesis. Xultophy® is therefore not recommended in these patients.

Hepatic/Biliary/Pancreatic
Pancreatitis
In clinical trials with Xultophy®, there were no confirmed cases of pancreatitis among Xultophy®-treated patients.

Use of GLP-1 receptor agonists has been associated with the risk of developing acute pancreatitis. For liraglutide, a component of Xultophy®, acute pancreatitis has been reported from clinical trials and marketed use. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Xultophy® should be discontinued; if acute pancreatitis is confirmed, Xultophy® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Acute Gallbladder Disease
In the LEADER trial, 3.1% of liraglutide-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholelithiasis or cholecystitis. The majority of events required hospitalization or cholecystectomy. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Immune
Antibody formation
Administration of Xultophy® may cause formation of antibodies against insulin degludec and/or liraglutide. In rare cases, the presence of such antibodies may necessitate adjustment of the

Xultophy® dose in order to correct a tendency to hyper- or hypoglycemia. Very few patients developed insulin degludec specific antibodies, antibodies cross-reacting to human insulin or anti-liraglutide antibodies following treatment with Xultophy®. Antibody formation has not been associated with reduced efficacy of Xultophy®.

Hypersensitivity and Allergic Reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock can occur with Xultophy®. Allergic reactions (manifested with signs and symptoms such as urticaria, rash, pruritus) have been reported with Xultophy®.

There have been post-marketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide, one of the components of Xultophy®. If a hypersensitivity reaction occurs, the patient should discontinue Xultophy® and other suspect medications and promptly seek medical advice.

Angioedema has also been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Xultophy®

Skin and Subcutaneous Tissue Disorders
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site from an affected to an unaffected area, and dose adjustment of antidiabetic medications may be considered.

Monitoring and Laboratory Tests
As with all insulin containing products, the need for regular blood glucose self-monitoring should be considered when using Xultophy® to obtain optimal glycemic control. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Ophthalmologic
Eye disorder
Intensification of therapy with insulin, a component of Xultophy®, with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Renal
Dehydration
Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in clinical trials with GLP-1 receptor agonists, including liraglutide, a component of Xultophy®. Patients treated with Xultophy® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Sexual Health
Fertility
There is no clinical experience with Xultophy® with respect to fertility. Animal reproduction

studies with insulin degludec have not revealed any adverse effects on fertility. A fertility study in rats has shown an increase in incidence of early embryonic death with liraglutide at 11 times the clinical exposure (see NON-CLINICAL TOXICOLOGY).

8.1 Special Populations

8.1.1 Pregnant Women

There is no clinical experience with use of Xultophy® in pregnant women. Animal reproduction studies with insulin degludec have not revealed any differences between insulin degludec and human insulin regarding embryotoxicity and teratogenicity. Animal studies with liraglutide have shown reproductive and developmental toxicity, including teratogenicity (see NON-CLINICAL TOXICOLOGY).

Xultophy® should not be used during pregnancy (see CONTRAINDICATIONS). If a patient wishes to become pregnant, or pregnancy occurs, treatment with Xultophy® should be discontinued.

8.1.2 Breast-feeding

There is no clinical experience with use of Xultophy® during breastfeeding. It is unknown whether insulin degludec or liraglutide is excreted in human milk. A study in lactating rats administered insulin degludec showed that insulin degludec was secreted in milk; the concentration in milk was lower than in plasma. Studies in lactating rats administered liraglutide also showed that liraglutide was excreted unchanged in milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for liraglutide in animal studies, women who are nursing should discontinue Xultophy® treatment.

8.1.3 Pediatrics

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

8.1.4 Geriatrics

Of the total number of the 1881 subjects in phase 3a clinical studies of Xultophy®, 375 (19.9%) were 65 and over, while 52 (2.8%) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. 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® cannot be ruled out.

Age had no clinically relevant effect on the pharmacokinetics of Xultophy® based on results from a population pharmacokinetic analysis including adult patients up to 83 years treated with Xultophy®.

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 recognise in the elderly (see WARNINGS AND PRECAUTIONS, hypoglycemia, ADVERSE REACTIONS and CLINICAL TRIALS).

8.1.5 Renal Impairment

Xultophy® can be used in patients with mild and moderate renal impairment. When Xultophy® is used in patients with mild or moderate renal impairment, glucose monitoring is to be intensified and the dose adjusted on an individual basis. Xultophy® cannot be recommended for use in patients with severe renal impairment including patients with end-stage renal disease. For more information see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY.

8.1.6 Hepatic Impairment

Xultophy® has not been studied in patients with hepatic impairment. For more information see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

In the clinical development programme Xultophy® did not show increased incidence of specific adverse reactions as compared to the two monocomponents insulin degludec and liraglutide.

The most frequently reported adverse reactions during treatment with Xultophy® were hypoglycemia and gastrointestinal adverse reactions, of which nausea was the most frequently reported and declined as treatment continued.

When pooling the 5 completed phase 3 trials, serious adverse events occurred rarely and with similar frequencies between treatment groups. Events were reported for 3.9% of subjects receiving Xultophy® versus 4.7%, 4.8% and 3.4% of subjects receiving basal insulin, GLP-1 RA and placebo treatment, respectively.

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

<u>Pool of Placebo and Active-Controlled Trials</u>
The safety of Xultophy® has been evaluated in clinical trials. The data in Table 4 reflect the exposure of 1881 patients to Xultophy® 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 m2 and 6.24% of the patients had an eGFR less than 60 mL/min/1.73 m^2.

Table 4: Treatment Emergent Adverse Reactions (possibly or probably related to Xultophy®) in Placebo and Active-Controlled Studies Reported in ≥1% of Patients Treated with Xultophy®

	Xultophy® N = 1881 (%)	Basal Insulins[1] N = 890 (%)	GLP-1 Receptor Agonists N = 557 (%)	Placebo N = 146 (%)
Gastrointestinal disorders				
Nausea	97 (5.2)	11 (1.2)	80 (14.4)	3 (2.1)
Diarrhea	65 (3.5)	8 (0.9)	39 (7.0)	2 (1.4)
Vomiting	29 (1.5)	5 (0.6)	29 (5.2)	1 (0.7)
Dyspepsia	24 (1.3)	1 (0.1)	12 (2.2)	0
Constipation	21 (1.1)	1 (0.1)	14 (2.5)	0
General disorders and administration site conditions				
Injection site bruising	21 (1.1)	5 (0.6)	7 (1.3)	1 (0.7)
Investigations				
Lipase increased	68 (3.6)	6 (0.7)	20 (3.6)	4 (2.7)
Metabolism and nutrition disorders				
Decreased appetite	46 (2.4)	4 (0.4)	26 (4.7)	0
Nervous system disorders				
Headache	23 (1.2)	9 (1.0)	11 (2.0)	1 (0.7)

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin and insulin containing products, including Xultophy® (see WARNINGS AND PRECAUTIONS). 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® 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 TRIALS), events of severe hypoglycemia were defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions (Table 5). Hypoglycemia episodes with a glucose level below 3.1 mmol/L associated with or without symptoms is shown in Table 5. No clinically important differences in risk of severe hypoglycemia between Xultophy® and comparators were observed in clinical trials.

Table 5: Hypoglycemia Episodes Reported in Xultophy®-Treated Patients with T2DM

	Patients naïve to basal insulin or GLP-1 receptor agonist			Patients currently on GLP-1 receptor agonist	Patients currently on basal insulin	
	DUAL I	**DUAL IV**	**DUAL IX**	**DUAL III**	**DUAL II**	**DUAL V**
	Xultophy®	**Xultophy®**	**Xultophy®**	**Xultophy®**	**Xultophy®**	**Xultophy®**
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 <3.1 mmol/L (%)	31.8*	41.3*	12.9**	31.6*	24.1*	28.4*

† episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
*Episodes of hypoglycemia with a glucose level below 3.1 mmol/L that are associated with or without symptoms of hypoglycemia.
** Episodes of hypoglycemia with a glucose level below 3.1 mmol/L that are associated with symptoms of hypoglycemia.

9.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse events were assessed as possibly or probably related by investigator at an incidence of <1% in placebo controlled clinical trials (in >1 patient, with higher frequency than placebo group) for Xultophy® in the clinical program.

Blood and lymphatic system disorders: anaemia
Eye disorders: retinopathy, vision blurred,
Gastrointestinal disorders: abdominal distension, abdominal discomfort, abdominal pain, gastritis, abdominal pain upper, flatulence, gastrooesophageal reflux disease, hyperchlorhydria, dry mouth, eructation, abdominal pain lower, colitis,
General disorders and administration site conditions: fatigue, asthenia, injection site reaction, early satiety, hunger, injection site mass injection site rash, local swelling, malasie, oedema peripheral,
Infections and infestations: gastroenteritis,
Investigations: amylase increased, weight increased, weight decreased, blood calcitonin increased, blood creatine phosphokinase increased, blood fibrinogen increased, brain natriuretic peptide increased, C-reactive protein increased, pancreatic enzymes increased, platelet count decreased,
Metabolism and nutrition disorders: hypoglycemia, hyperphagia,
Musculoskeletal and connective tissue disorders: arthralgia, myalgia,
Nervous system disorders: dysgeusia, hypoglycaemic unconsciousness, migraine, paraesthesia,
Renal and urinary disorders: haematuria,
Respiratory, thoracic and mediastinal disorders: cough, dyspnoea
Skin and subcutaneous tissue disorders: hyperhidrosis, skin induration,
Vascular disorders: haematoma, hypotension,

Few cases of cholecystitis and cholelithiasis have been reported in the clinical trials with Xultophy®. These events were also reported in clinical trials with liraglutide 1.8 mg.

9.4 Post-Market Adverse Reactions

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

- Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia 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

10 DRUG INTERACTIONS

10.1 Overview

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulins therapies. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs or losing potassium through other means (e.g. diarrhea) (See ADVERSE REACTIONS). Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Thiazolidinediones (TZDs), alone or in combination with other anti-diabetic agents (including insulin), can cause heart failure and edema. The combination of insulin with a TZD is not indicated for the treatment of type 2 diabetes mellitus. Please refer to the respective TZD product monograph, (see WARNINGS AND PRECAUTIONS), information when the use of these drugs in combination with any insulin-containing product, including Xultophy®, is contemplated.

10.2 Drug-Drug Interactions

Interaction studies with Xultophy® have not been performed. A number of medications affect glucose metabolism and may require dose adjustment of Xultophy® and particularly close monitoring.

Drugs that may affect glucose metabolism:

Drugs that may increase the blood-glucose-lowering effect of Xultophy® and susceptibility to hypoglycemia:
Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), sulfonamide antibiotics, GLP-1 receptor agonists, DDP-4 inhibitors, SGLT-2 inhibitors.

Drugs that may reduce the blood-glucose-lowering effect of Xultophy®:
Corticosteroids, danazol, diuretics, glucagon, isoniazid, niacin, phenothiazine derivatives, oral contraceptives, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, salbutamol, terbutaline),

thyroid hormones, and atypical antipsychotics (e.g., olanzapine and clozapine).

Drugs or substances that may increase or decrease the blood-glucose-lowering effect of Xultophy®:
Beta-blockers, clonidine, lithium salts, and alcohol

Drugs that may blunt the signs and symptoms of hypoglycemia:
Sympatholytic medicinal products, such as beta-blockers, clonidine, guanethidine, and reserpine,

Drugs that may be affected by slower gastric emptying effect of liraglutide:
The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption.

Specific drug-drug interactions with 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 C_{max} of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Warfarin and other coumarin derivatives
No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR (International Normalised Ratio) is recommended.

Paracetamol (Acetaminophen)
Liraglutide did not change the overall exposure (AUC) of paracetamol following a single dose of 1,000 mg. Paracetamol C_{max} was decreased by 31% and median t_{max} was delayed up to 15 min.

Atorvastatin
Liraglutide did not change the overall exposure (AUC) of atorvastatin following a single-dose administration of atorvastatin 40 mg. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin
Liraglutide did not change the overall exposure (AUC) of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C_{max} increased by 37% while median t_{max} did not change.

Digoxin
A single dose administration of digoxin 1 mg with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximum concentration (t_{max}) was delayed from 1 h to 1.5 h.

Lisinopril
A single-dose administration of lisinopril 20 mg with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median t_{max} was delayed from 6 h to 8 h with liraglutide.

Oral contraceptives
Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was 1.5 h later with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure (AUC) of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Combination with Insulin
No pharmacokinetic interaction was observed between liraglutide and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Units/kg (single-dose) and liraglutide 1.8 mg (steady state) were administered in patients with type 2 diabetes.

Drugs that Increase Heart Rate
Liraglutide causes an increase in heart rate. The impact on the heart rate of co-administration of liraglutide with other drugs that increase heart rate, (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of liraglutide with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation
Liraglutide causes an increase in the PR interval. The impact on the PR interval of co-administration of liraglutide with other drugs that prolong the PR interval (including calcium channel blockers, beta-adrenergic blockers, digitalis glycosides, and HIV protease inhibitors) has not been evaluated in drug-drug interaction studies. As a result, co-administration of liraglutide with these drugs should be undertaken with caution.

10.3 Drug-Food Interactions

Interaction with food has not been established.

10.4 Drug-Herb Interactions

Interaction with herbal products has not been established.

10.5 Drug-Laboratory Test Interactions

Interaction with laboratory tests has not been established.

10.6 Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia (see OVERDOSAGE).

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Xultophy® is a combination product consisting of insulin degludec and liraglutide.

<u>Insulin degludec</u>
Insulin degludec is a basal insulin that binds specifically to the human insulin receptor and

results in the same pharmacological effects as human insulin. Insulin and its analogues 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) analogue that stimulates glucose-dependent insulin secretion, lowers glucagon secretion, and slows gastric emptying.

11.2 Pharmacodynamics

Following a single-dose administration, Xultophy® has a duration of action reflecting the combination of the individual action profiles of insulin degludec and liraglutide. Following once-daily administration, Xultophy® lowers fasting plasma glucose levels and postprandial blood glucose levels.

Cardiac Electrophysiology (QTc)
The effect of Xultophy® on QTc has not been studied.

Liraglutide
The effect of liraglutide, one of the components of Xultophy®, on cardiac repolarization was tested in a QTc study. Liraglutide at 1.2 mg and 1.8 mg doses was associated with statistically significant shortening of the QTc interval at most post-dose time points. The clinical significance of an acquired, drug-induced QTc shortening of this magnitude is not known.

11.3 Pharmacokinetics

Overall the pharmacokinetics of insulin degludec and liraglutide were not affected in a clinically relevant manner when administered as Xultophy®.

The following reflects the pharmacokinetic properties of Xultophy® unless stated that the presented data is from administration of insulin degludec or liraglutide alone.

Absorption: Following a single-dose administration in healthy subjects, the overall exposure of insulin degludec was equivalent following administration of Xultophy® versus insulin degludec alone while the C_{max} was higher by 12%. The overall exposure of liraglutide was comparable following administration of Xultophy® versus liraglutide alone while C_{max} was lower by 23%.
In patients with type 2 diabetes (mean body weight 87.5 kg) reaching the maximum daily dose (50 units/1.8 mg) of Xultophy®, the estimated mean steady-state exposure ($AUC_{0\text{-}24h}$) of insulin degludec was 113 h*nmol/L and of liraglutide 327 h*nmol/L based on a population pharmacokinetic analysis. The corresponding maximum concentrations were 5196 pmol/L for insulin degludec and 14791 pmol/L for liraglutide. Steady-state concentrations of insulin degludec and liraglutide are reached after 2-3 days of daily administration.

Insulin degludec and liraglutide exposure increased proportionally with the Xultophy® dose within the full dose range based on a population pharmacokinetic analysis.

The pharmacokinetic profile of Xultophy® is consistent with once daily dosing and steady-state concentration of insulin degludec and liraglutide is reached after 2-3 days of daily administration.

Distribution: Insulin degludec and liraglutide are extensively bound to plasma proteins (>99% and >98%, respectively).

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

Liraglutide
During a 24-hour period following administration of a single radiolabelled [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (<9% and <5% of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.

Elimination: At steady-state, the half-life of insulin degludec is approximately 25 hours and the half-life of liraglutide is approximately 13 hours, based on previous studies of insulin degludec (Tresiba®) and liraglutide (Victoza®).

Special Populations and Conditions

Pediatrics: No studies have been performed with Xultophy® in children and adolescents below 18 years of age.

Geriatrics: Age had no clinically relevant effect on the pharmacokinetics of Xultophy® based on results from a population pharmacokinetic analysis including adult patients up to 83 years treated with Xultophy®.

Sex: Gender had no clinically relevant effect on the pharmacokinetics of Xultophy® based on results from a population pharmacokinetic analysis.

Pregnancy and Breast-feeding: <text>

Genetic Polymorphism: <text>

Ethnic origin: Race had no clinically relevant effect on the pharmacokinetics of Xultophy® based on results from a population pharmacokinetic analysis including patients with different ethnic origins.

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

Liraglutide
Subjects with varying degrees of hepatic insufficiency displayed a reduced exposure to liraglutide. After a single-dose, the AUC in mild (Child Pugh score 5-6), moderate, and severe

(Child Pugh score > 9) compared to healthy subjects was lower on average by 23%, 13% and 44% respectively

Renal Insufficiency:
Insulin degludec
Pharmacokinetics of insulin degludec was studied in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 U/kg) of insulin degludec. Renal function was defined using creatinine clearance (Clcr) as follows: ≥ 90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and < 30 mL/min (severe).

Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0-120h,SD}$) and peak exposure of insulin degludec were on average about 10-25% and 13-27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of insulin degludec ($CL/F_{IDeg,SD}$) in subjects with ESRD (see WARNINGS AND PRECAUTIONS).

Liraglutide
Subjects with varying degrees of renal insufficiency displayed a reduced exposure to liraglutide. After a single-dose, the AUC in mild (CrCL 50-80 mL/min), moderate (CrCL 30-50 mL/min), severe (CrCL < 30 mL/min) and end-stage renal disease requiring dialysis compared to healthy subjects was lower on average by 33%, 14%, 27% and 26%, respectively (see WARNINGS AND PRECAUTIONS).

Body Weight: The effect of body weight on the exposure level of the components of Xultophy® was investigated in a population pharmacokinetic analysis. Exposure of insulin degludec and liraglutide was inversely correlated with body weight.

12 STORAGE, STABILITY AND DISPOSAL

Prior to first use, Xultophy® should be stored between 2°C and 8°C 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® if it has been frozen.

After first use, the Xultophy® pen can be stored for 21 days at controlled room temperature (below 30°C) or in a refrigerator (2°C to 8°C). Keep all Xultophy® pens away from direct heat and light.

The storage conditions are summarized in Table 6:

Table 6: Storage Conditions for Xultophy® pen

Prior to first use	After first use	
Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
Until expiration date	21 Days	

13 SPECIAL HANDLING INSTRUCTIONS

Always remove the needle after each injection and store the Xultophy® pen without a needle attached. This prevents contamination and/or infection, or leakage of the Xultophy® pen, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Each Xultophy® pen is for use by a single patient. The Xultophy® pen should never be shared between patients, even if the needle is changed.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

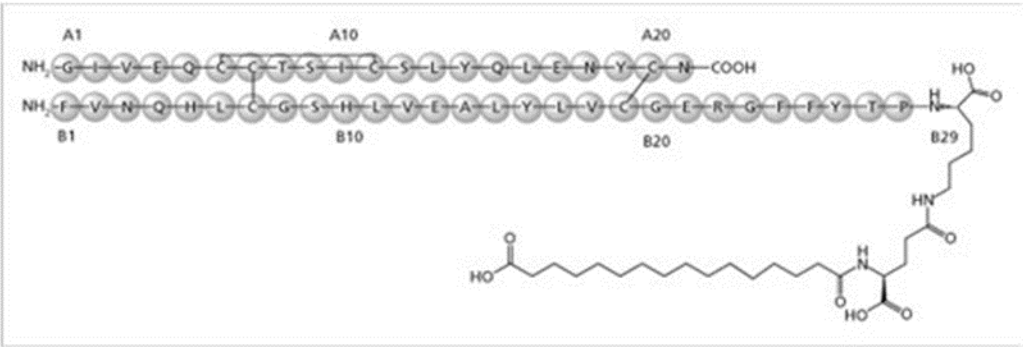
Proper name: Xultophy®

Chemical name: Insulin degludec and liraglutide

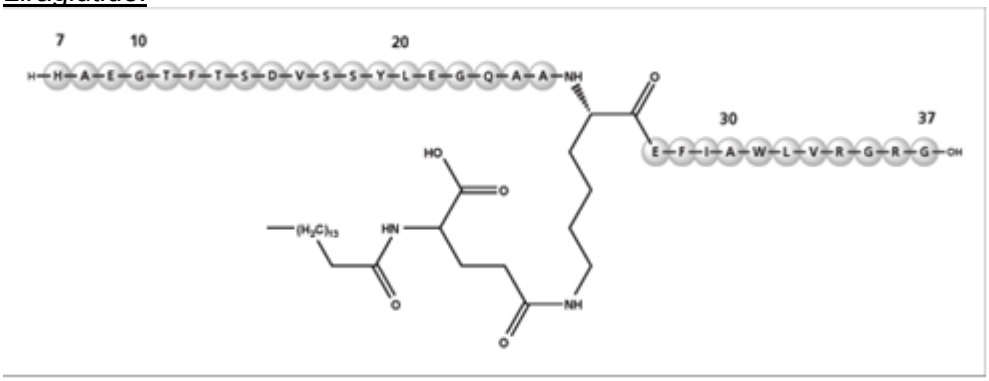
Molecular formula and molecular mass:
Insulin degludec:
$C_{274}H_{411}N_{65}O_{81}S_6$ and 6103.97 dalton

Liraglutide:
$C_{172}H_{265}N_{43}O_{51}$ and 3751.20 dalton

Structural formula:
Insulin degludec:



Liraglutide:



Physicochemical properties: Xultophy® is a sterile, aqueous, clear, and colorless solution. Each mL contains 100 units insulin degludec and 3.6 mg liraglutide. Each pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 10.8 mg liraglutide.

Product Characteristics

Xultophy® (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 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-hexadecandioyl-γ-Glu) des(B30) human insulin).

Liraglutide is an analogue 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 of the peptide precursor.

Xultophy® pens are designed to deliver doses from1 to 50 in a single injection with dose increments of 1 (each increment contains 1 unit insulin degludec and 0.036 mg liraglutide).

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

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.

An overview of the trials pertaining to the authorized indication can be found in

Table 7.Three trials (3697, 3951 and 4229) were conducted in adult subjects inadequately controlled on one or more oral anti-diabetic drugs (OADs) (e.g. metformin, pioglitazone, sulfonylurea, or sodium-glucose cotransporter-2 inhibitors (SGLT2i). Two trials (3912 and 3952) included adult subjects with type 2 diabetes who were inadequately controlled on metformin (±sulfonylurea±glinides) and basal insulin. One study, Study 3851, was conducted in subjects converting from liraglutide (with doses up to 1.8 mg). Subjects remained on background medications in all trials. In these trials (n=3908), mean duration of diabetes was 8.8 years, mean BMI was 31.8, 52.2 % were male, 75.2% were white, 17.8% were Asian, and 5.5% were black.

In all trials, Xultophy® was titrated twice weekly by increments or decrements of 2 units, as shown in
Table **8** towards a pre-specified fasting blood glucose target. The same titration algorithm was applied for basal insulin comparators. In Study 3912, titration in the comparator arm was limited by a maximum dose of 50 units of insulin degludec.

Table 7: Summary of trial design and patient demographics

Study #	Trial design and duration	Dosage, and route of administration	Background Therapy	Study subjects (n = number)	Mean age (Range)	Gender
3697 DUAL I	26 Weeks; Multi-centre, multi-national randomized (2:1:1), open-label, three-arm, parallel group, treat-to-target trial comparing Xultophy® to IDeg and liraglutide in subjects inadequately controlled on metformin ± pioglitazone.	**Xultophy®:** Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. Maximum does of 50 units. S.C **IDeg:** Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. No pre-defined maximum dose. S.C. **Liraglutide:** Weekly dose increase of 0.6 mg/day until reaching the maintenance dose of 1.8 mg/day. S.C.	**Metformin:** ≥ 1500 mg/day or maximum tolerated dose. Oral **Pioglitazone:**≥ 30 mg/day. Oral	**Xultophy®:** n=833 **IDeg:** n=413 **Liraglutide:** n=414 **Total:** n=1660	**Xultophy®:** 55.1 (27.8-83.8) **IDeg:** 54.9 (24.0-79.1) **Liraglutide:** 55.0 (24.4-81.6) **Total:** 55.0 (24.0-83.8)	**Xultophy®:** Male: 435 Female: 398 **IDeg:** Male: 200 Female: 213 **Liraglutide:** Male: 208 Female: 206 **Total:** Male: 843 Female: 817
3951 DUAL IV	26 Weeks, Multi-centre, multi-national randomised (2:1), double-blind, two-arm, parallel group, treat-to-target trial comparing Xultophy® to placebo in insulin naïve T2DM subjects inadequately controlled on sulphonylurea ± metformin.	**Xultophy®:** Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. though with a titration target of 4-6 mmol/L. Maximum does of 50 units. S.C **Placebo:** Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. though with a titration target of 4-6 mmol/L. Maximum does of 50 units. S.C	**Sulphonylurea:** Half maximum approved dose according to local label. Oral **Metformin:** ≥ 1500 mg/day or maximum tolerated dose. Oral	**Xultophy®:** n=289 **Placebo:** n=146 **Total:** n=435	**Xultophy®:** 60.0 (27.6-87.0) **Placebo:** 59.4 (27.3-84.5) **Total:** 59.8 (27.3-87.0)	**Xultophy®:** Male: 154 Female: 135 **Placebo:** Male: 73 Female: 73 **Total:** Male:227 Female:208
4229 DUAL IX	26 Weeks, Multi-centre, multi-national randomized (1:1), open-label, two-arm, parallel, treat-to-target trial comparing Xultophy® to IGlar in T2DM subjects inadequately controlled on SGLT2i ± other OADs.	**Xultophy®**: Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. Maximum dose of 50 units. S.C **IGlar:** Starting dose of 10 units dosed once daily and titrated twice weekly according to Table **8**. No pre-defined maximum dose. S.C	**SGLT2i:** Continued at unchanged pre-trial doses. Oral **Metformin:** Continued at unchanged pre-trial doses. Oral **Pioglitazone:** Continued at unchanged pre-trial doses. Oral	**Xultophy®:** n=210 **IGlar:** n=210 **Total:** n=420	**Xultophy®:** 56.1 (25-83) **IGlar:** 57.2 (30-82) **Total:** 56.7 25-83	**Xultophy®:** Male: 121 Female: 89 **IGlar:** Male: 126 Female: 84 **Total:** Male:247 Female:173

Study #	Trial design and duration	Dosage, and route of administration	Background Therapy	Study subjects (n = number)	Mean age (Range)	Gender
3851 DUAL III	26 Weeks; Multi-centre, multi-national randomised (2:1), open-label, two-arm, parallel group, treat-to-target trial comparing Xultophy® to a continued pre-trial regimen of GLP-1 RA* both in combination with metformin±pioglitazone±SU in insulin naïve T2DM subjects inadequately controlled on GLP-1 RA (liraglutide or exenatide). *In Table 12 only data from subjects treated with liraglutide at baseline are include.	**Xultophy®:** Starting dose of 16 units dosed once daily and titrated twice weekly according to Table **8**. Maximum dose of 50 units. S.C **GLP-1 RA:** Maximum tolerated dose or maximum dose according to local label. S.C	Metformin (oral) Maximum tolerated dose or maximum dose according to local label. Oral	**Xultophy®:** n=292 **GLP-1 RA:** n=146 **Total:** n=438	**Xultophy®:** 58.3 (22.0-77.9) **GLP-1 RA:** 58.4 (37.8-78.3) **Total:** 58.3 (22.0-78.3)	**Xultophy®:** Male: 153 Female: 139 **GLP-1 RA:** Male: 71 Female: 75 **Total:** Male: 224 Female: 214
3952 DUAL V	26 Weeks; Multi-centre, multi-national, randomised (1:1), open-label, two-arm, parallel group, treat-to-target trial comparing Xultophy® + metformin to IGlar + metformin in T2DM subjects inadequately controlled on IGlar at a daily dose between 20 and 50 units (both inclusive) in combination with metformin.	**Xultophy®**: Starting dose of 16 units dosed once daily and titrated twice weekly according to Table **8**. Maximum dose of 50 units. S.C **IGlar:** Starting dose equal to pre-trial daily dose of IGlar and titrated twice weekly according to Table **8**. No pre-defined maximum dose. S.C	Metformin (oral) Maximum tolerated dose or maximum dose according to local label. Oral	**Xultophy®:** n=278 **IGlar:** n=279 **Total:** n=557	**Xultophy®:** 58.4 (29.2-81.7) **IGlar:** 59.1 (27.6-80.4) **Total:** 58.8 (27.6-81.7)	**Xultophy®:** Male: 143 Female: 135 **IGlar:** Male: 137 Female: 142 **Total:** Male: 280 Female: 277
3912 DUAL II	26 Weeks; Multi-centre, multi-national randomised (1:1), double-blind, two-arm, parallel group, treat-to-target trial comparing Xultophy® + metformin to IDeg + metformin in T2DM subjects inadequately controlled on basal insulin (20-40 units) + metformin ± sulphonylurea or glinides.	**Xultophy®:** Starting dose of 16 units of Xultophy® dosed once daily and titrated twice weekly according to Table **8**. The maximum dose of Xultophy® was 50 units. S.C. **IDeg:** Starting dose of 16 units of IDeg, dosed once daily and titrated twice weekly according to Table **8**. The maximum dose of IDeg in the comparator arm was 50 units. S.C	Metformin: ≥ 1500 mg/day or maximum tolerated dose. Oral	**Xultophy®:** n=199 **IDeg:** n=199 **Total:** n=398	**Xultophy®:** 56.8 (31.4-76.9) **IDeg:** 57.5 (29.5-85.8) **Total**: 57.2 (29.5-85.8)	**Xultophy®:** Male: 112 Female: 87 **IDeg:** Male:106 Female: 93 **Total:** Male:218 Female:180

Abbreviations: IDeg = insulin degludec; IGlar = insulin glargine; OD = once-daily; S.C.= subcutaneous; T2DM = type 2 diabetes mellitus; GLP-1 RA = GLP-1 receptor agonist

Table 8: Titration of Xultophy® and basal insulin

Pre-breakfast plasma glucose*		***Dose adjustment***	
mmol/L	mg/dL	*Xultophy® (units)*	*Basal insulin (units)*
< 4.0	< 72	*-2*	*-2*
4.0-5.0	72-90	*0*	*0*
> 5.0	> 90	*+2*	*+2*

15.2 Study Results

Patients with Type 2 Diabetes Uncontrolled on OAD Treatment:

Trial 3697 (DUAL I)

The efficacy and safety of Xultophy® compared to insulin degludec and liraglutide, all administered once-daily, was studied in a 26-week randomized, open-label, three-arm parallel trial in 1660 patients with type 2 diabetes mellitus inadequately controlled on 1-2 OADs (metformin or metformin with or without pioglitazone).

The starting dose of Xultophy® was 10 units (10 units insulin degludec and 0.36 mg liraglutide). The starting dose of insulin degludec was 10 units. Xultophy® and insulin degludec were titrated twice weekly towards a target fasting blood glucose goal of 4-5mmol/L. Patients in the liraglutide arm followed a fixed dose escalation scheme with a starting dose of 0.6 mg and a dose increase of 0.6 mg weekly until a daily dose of 1.8 mg was reached. Patients continued on pre-trial treatment with metformin or metformin and pioglitazone throughout the trial.

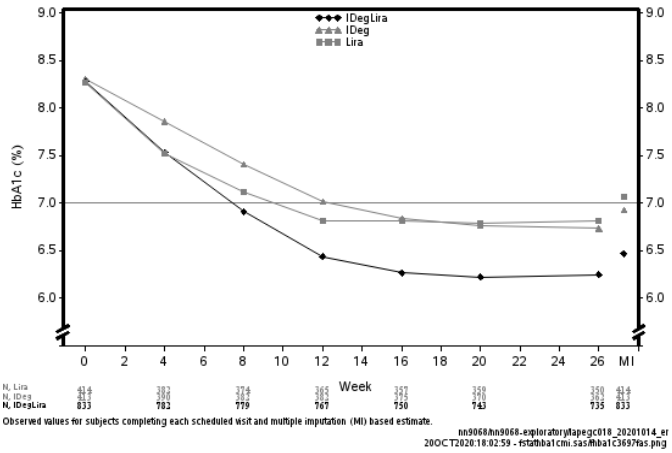
At the end of 26 weeks, treatment with Xultophy®, insulin degludec, and liraglutide resulted in a reduction in HbA1c from baseline of 1.81%, 1.35% and 1.21%, respectively, (see

Table 9 and Figure 1). The end of trial dose of Xultophy® was 38 units (38 units insulin degludec and 1.37 mg liraglutide).

Table 9 Results of a 26 week trial with Xultophy® in patients with type 2 diabetes mellitus inadequately controlled on metformin alone or in combination with pioglitazone (Trial 3697, DUAL I)

	Previous treatment with OADs		
	Xultophy® + metformin ±pioglitazone	**Insulin degludec + metformin ± pioglitazone**	**Liraglutide + metformin ± pioglitazone**
N	833	413	414
HbA_{1c} (%) Baseline→End of trial# LS mean change# *Estimated difference* [95% CI]#* *p-value*	 8.3→6.5 -1.81	 8.3→6.9 -1.35 *-0.46% [-0.59; -0.34]* *<0.0001*[A]	 8.3→7.1 -1.21 *-0.60% [-0.72; -0.47]*[A] *<0.0001*[A]
Patients achieving HbA_{1c} <7%**	74.1%	60.5%	56.0%
FPG (mmol/L) Baseline→End of trial# LS mean change#	 9.2→5.8 -3.43	 9.4→5.9 -3.29	 9.0→7.4 -1.80

[A] Primary endpoint was tested for non-inferiority of Xultophy® to insulin degludec based on a pre-specified non-inferiority margin of 0.3% and for superiority of Xultophy® to liraglutide. The primary objective was fulfilled only if both non-inferiority and superiority were confirmed.
Estimated using an ANCOVA method with treatment, baseline HbA1c stratum, sub-study, concomitant diabetes treatment and country 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 value at week 26 data were considered non-responders.
There were 11.8% of subjects in the Xultophy® arm, 12.3% in the insulin degludec arm and 15.5% in the liraglutide arm for whom HbA1c data was missing at week 26.



IDegLira=Xultophy®, IDeg=insulin degludec, Lira=Liraglutide
Figure 1: Mean HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on liraglutide (Trial 3697, DUAL I)

Trial 3951 (DUAL IV)

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

Xultophy® was started at 10 units (10 units insulin degludec and 0.36 mg liraglutide) and titrated twice weekly towards a target fasting blood glucose goal of 4-6mmol/L. Patients continued on

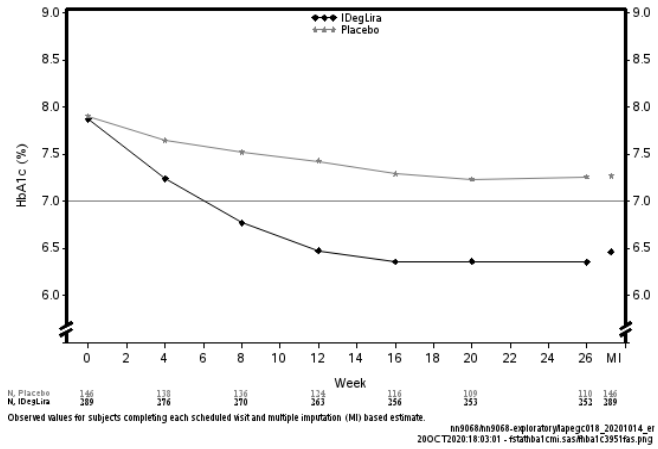
pre-trial treatment with sulfonylurea, with or without metformin throughout the trial.

Treatment with Xultophy® for 26 weeks resulted in a statistically significant reduction in mean HbA1c compared to placebo (see Table 10 and Figure 2). The end of trial dose of Xultophy® was 28 units (28 units insulin degludec and 1.01 mg liraglutide).

Table 10 Results of a 26 week trial with Xultophy® in patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or in combination with metformin (Trial 3951, DUAL IV)

	Previous treatment with OADs	
	Xultophy® + sulfonylurea ± metformin	**Placebo + sulfonylurea ± metformin**
N	289	146
HbA_{1c} (%) Baseline→End of trial# LS mean change *Estimated difference [95% CI]#* *p-value*	 7.9→6.5 -1.42	 7.9→7.3 -0.62 *-0.81 [-0.98; -0.63]* <0.0001[A]
Patients achieving HbA_{1c} <7%**	70.9%	26.7%
FPG (mmol/L) Baseline→End of trial# LS mean change#	 9.1→6.6 -2.56	 9.1→8.5 -0.67

[A] Primary endpoint was tested for superiority of Xultophy® to placebo.
Estimated using an ANCOVA with treatment, region and pre-trial medication as fixed factors and baseline response as covariate. Multiple imputation modelled "jump-to-control" of the treatment effect for subjects having missing week 26 data.
** Patients with missing HbA1c value at week 26 data were considered non-responders.
There were 12.8% of subjects in the Xultophy® arm and 24.7% in the placebo arm for whom HbA1c data was missing at week 26.



IDegLira=Xultophy®

Figure 2: Mean HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on sulphonylurea alone or in combination with metformin (Trial 3951, DUAL IV)

<u>Trial 4229 (DUAL IX)</u>

The efficacy and safety of Xultophy® compared to insulin glargine U-100, both administered once-daily, were studied in a 26-week randomized, open-label, two-arm parallel trial in 420

patients with type 2 diabetes mellitus inadequately controlled on a sodium-glucose cotransporter 2 inhibitors (SGLT2i) alone or in combination with other OADs (with or without metformin, pioglitazone, and/or dipeptidyl peptidase-4 [DPP4] inhibitor). At randomization, the DPP4 inhibitor was discontinued.

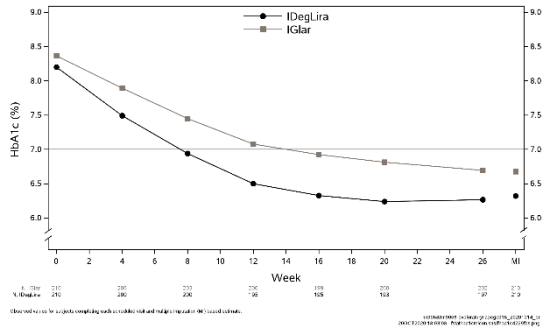
The starting dose of Xultophy® was 10 units (10 units insulin degludec and 0.36 mg liraglutide). The starting dose of insulin glargine U-100 was 10 units. Xultophy® and insulin glargine U-100 were titrated twice weekly to target a fasting blood glucose goal of 4-5mmol/L. Patients could not increase the dose of Xultophy® 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 mean fasting self-measured blood glucose goal was achieved by 49.0% of patients randomized to Xultophy® and 41.9% of patients randomized to insulin glargine at 26 weeks.

At the end of 26 weeks, Xultophy® resulted in a reduction in HbA1c from baseline of 1.95% and insulin glargine U-100 resulted in a reduction of 1.61% (see Table 11 and Figure 3). At the end of trial, the average dose of Xultophy® was 36 units (36 units insulin degludec and 1.01 mg liraglutide) and the dose of insulin glargine was 54 units; 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 11 Results of a 26-Week Trial in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on SGLT2i alone or in combination with Metformin, Pioglitazone and/or DPP4 Inhibitor (Trial 4229, DUAL IX)

	Previous treatment with OADs	
	Xultophy® + SGLT2i ± metformin± pioglitazone	**Insulin Glargine U-100 + SGLT2i ± metformin± pioglitazone**
N	210	210
HbA_{1c} (%) Baseline→End of trial# LS mean change# *Estimated difference [95% CI]#* p-value	 8.2→6.3 -1.95	 8.4→6.7 -1.61 *-0.34 [-0.48; -0.20]* <0.0001[A]
Patients achieving HbA_{1c} <7%*, ##	79.5%	68.6%
FPG (mmol/L) Baseline→End of trial# LS mean change#	 9.5 → 5.8 -3.78	 9.6 →6.1 -3.46

[A]Primary endpoint was tested for non-inferiority of Xultophy® to insulin glargine based on a pre-specified non-inferiority margin of 0.3%.
Estimated using an ANCOVA with treatment, pre-trial OAD and region as factors and corresponding baseline value as covariate. Data obtained after premature treatment discontinuation are included in the analysis. Missing data were imputed using conditional reference based multiple imputation including data obtained after premature treatment discontinuation.
Patients with missing HbA1c value at week 26 data were considered non-responders.
There were 6.2% of subjects in the Xultophy® arm and 3.8% in the insulin glargine arm for whom HbA1c data was missing at week 26.



IDegLira=Xultophy®

Figure 3: Mean HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on GLP-1 receptor agonists (Trial 4229, DUAL IX)

Patients currently on basal insulin or GLP-1 receptor agonist:

Trial 3851 (DUAL III)

Conversion from GLP-1 receptor agonist to Xultophy®

The efficacy and safety of Xultophy® (once-daily) compared to unchanged pre-trial liraglutide up to a dose of 1.8 mg daily was studied in a 26-weeks randomised, open-label, treat-to-target trial in patients with type 2 diabetes mellitus inadequately controlled on a maximum approved or tolerated dose of liraglutide and metformin alone (74.2%) or in combination with pioglitazone (2.5%), sulphonylurea (21.2%) or both (2.1%). Oral anti-diabetic drugs (OADs) were continued at pre-trial doses and dosing frequency throughout the trial.

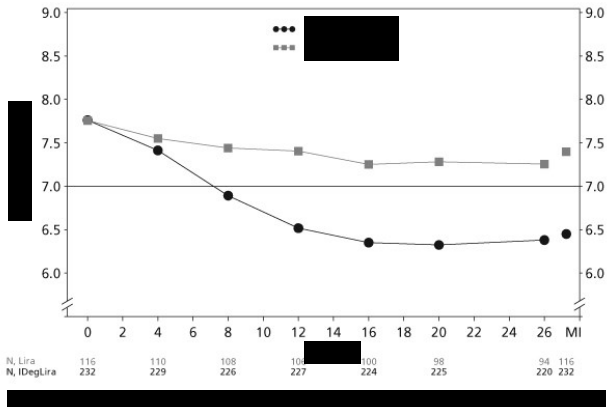
When transferring from liraglutide, the starting dose of Xultophy® was 16 units (16 units insulin degludec and 0.6 mg liraglutide) and the dose was titrated twice weekly according to Table **8**. The end of trial dose of Xultophy® was 43 units (43 units insulin degludec/1.6 mg liraglutide). For patients who remained on unchanged pre-trial liraglutide, the average starting dose was 1.7 mg. The primary endpoint, change in HbA1c, was tested for superiority of Xultophy® to unchanged liraglutide therapy.

Treatment with Xultophy® resulted in a statistically significant reduction in HbA1c at 26 weeks from baseline compared to unchanged liraglutide therapy (see Table 12 and Figure 4). The trial was designed to investigate the distinct efficacy and safety associated with transfer of therapy to Xultophy® in subjects treated with liraglutide and in need of treatment intensification, and this was the rationale for continuing unchanged pre-trial therapy in the arm not receiving Xultophy®. However, insulin naïve subjects inadequately controlled on liraglutide and in need of treatment intensification would not remain on unchanged liraglutide in clinical practice. Hence, the difference in HbA1c effect observed in the trial may not reflect the effect that will be observed in the care setting where insulin naïve subjects inadequately controlled on liraglutide and in need of treatment intensification would receive additional therapy.

Table 12: Results of a 26 week trial with Xultophy® in patients with type 2 diabetes mellitus inadequately controlled on liraglutide up to 1.8 mg daily (Trial 3851, DUAL III)

	Previous treatment with liraglutide	
	Xultophy®	**Liraglutide**
N	232	116
HbA_{1c} (%) Baseline→End of trial LS mean change# *Estimated difference [95% CI]#* *p-value*	 7.8→6.4 -1.34	 7.8→7.4 -0.42 *-0.92[A][-1.11; -0.73]* *p<0.001*
Patients achieving HbA_{1c} <7%##	74.6%	30.2%
FPG (mmol/L) Baseline→End of trial LS mean change#	 8.9→6.1 -2.94	 9.4→8.7 -0.71

[A] Endpoint with confirmed superiority of Xultophy® vs. Liraglutide. The trial was designed to investigate the distinct efficacy and safety associated with transfer of therapy to Xultophy® in subjects treated with liraglutide and in need of treatment intensification, and this was the rationale for continuing unchanged pre-trial therapy in the arm not receiving Xultophy®. However, insulin naïve subjects inadequately controlled on liraglutide and in need of treatment intensification would not remain on unchanged liraglutide in clinical practice. Hence, the difference in HbA1c effect observed in the trial may not reflect the effect that will be observed in the care setting where insulin naïve subjects inadequately controlled on liraglutide and in need of treatment intensification would receive additional therapy.
Estimated using an ANCOVA with treatment, pre-trial liraglutide treatment and region as fixed factors and baseline response as covariate. Multiple imputation modelled "jump to reference" of the treatment effect for subjects having missing week 26 data.
Patients with missing HbA1c data at week 26 were considered as non-responders. There were 5.2% of subjects in the Xultophy® arm and 19.0% in the liraglutide arm for whom HbA1c data was missing at week 26.



IDegLira=Xultophy®

Figure 4: Mean HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on liraglutide (Trial 3851, DUAL III)

Trial 3952 (DUAL V)
Conversion from insulin glargine

The efficacy and safety of Xultophy® compared to insulin glargine, both once daily and added to metformin, were studied in a 26-week randomised, open-label, treat-to-target trial in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine (20-50 units) and metformin. The patients were randomised to two arms. In one arm, patients were switched from once-daily insulin glargine to once-daily Xultophy® at a starting dose of 16 units. In the other arm, patients continued insulin glargine with the starting dose equal to the pre-trial daily dose. The average starting dose of insulin glargine U-100 was 32 units. The dose was titrated twice

weekly according to
Table **8**, but patients could not increase the dose of the two products by more than 4 units per week. The maximum allowed dose was 50 units for Xultophy®, while there was no maximum dose for insulin glargine. The targeted fasting plasma glucose goal was achieved in 39.6% of patients randomized to insulin glargine and 32.9% of the patients randomized to Xultophy® at 26 weeks. The primary endpoint, change in HbA1c, was tested for non-inferiority and superiority once non-inferiority was demonstrated of Xultophy® compared to insulin glargine.

At the end of 26 weeks, treatment with Xultophy® was non-inferior to insulin glargine based on a non-inferiority margin of 0.3%. At the end of trial, the average dose of Xultophy® was 41 units (41 units insulin degludec/1.5 mg liraglutide), and the dose of insulin glargine was 66 units, and it is unclear that these observed differences in insulin doses are clinically important. The difference in HbA1c 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.

Table 13: Results of a 26 week trial with Xultophy® in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine (Trial 3952, DUAL V)

	Previous treatment with basal insulin	
	Xultophy® (Switched from insulin glargine)	**Insulin glargine**
N	278	279
HbA_{1c} (%) Baseline→End of trial LS mean change# *Estimated difference [95% CI]#* p-value for superiority	 8.4→6.6 -1.83	 8.2→7.1 -1.22 *-0.62[A][-0.76; -0.48]* *p<0.001*
Patients achieving HbA_{1c} <7%##	68.3%	46.2%
Rate of confirmed hypoglycemia* per patient year of exposure (percentage of patients)	2.23 (28.4%)	5.05 (49.1%)
Body Weight (kg) Baseline→End of trial LS Mean change#	 88.3→86.9 -1.23	 87.3→89.1 1.88
FPG (mmol/L) Baseline→End of trial LS mean change#	 8.9→6.1 -3.05	 8.9→6.1 -2.87

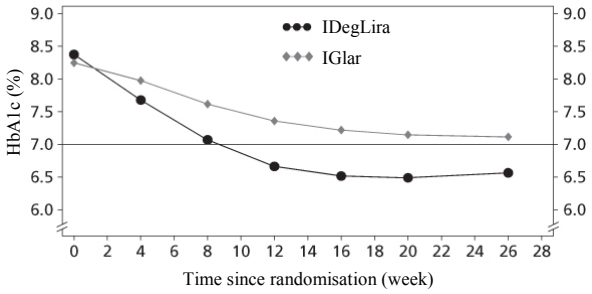
[A] Confirmed superiority of Xultophy® vs Insulin glargine. The difference in glucose lowering effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where alternative insulin glargine dosage can be used.

The primary endpoint (HbA1c) was tested for superiority once non-inferiority (limit of 0.3%) was demonstrated.

Estimated using an ANCOVA with treatment and region as fixed factors and baseline response as covariate. Multiple imputation modelled "jump to reference" of the treatment effect for subjects having missing week 26 data.

Patients with missing HbA1c value at week 26 data were considered non-responder. There were 10.1% of subjects in the Xultophy® arm and 4.7% in the insulin glargine arm for whom HbA1c data was missing at week 26.

*Confirmed hypoglycemia defined as severe hypoglycemia (episode requiring assistance of another person) and/or minor hypoglycemia (plasma glucose<3.1 mmol/L irrespective of symptoms.



IDegLira=Xultophy®, IGlar = insulin glargine

Figure 5: HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine (Trial 3952, DUAL V)

Trial 3912 (DUAL II)

Conversion from basal insulin therapies

The efficacy and safety of Xultophy® compared to insulin degludec, both once daily and added on to metformin, were studied in a 26-weeks randomised, double-blind, treat-to-target trial in patients with type 2 diabetes mellitus inadequately controlled on basal insulin (20-40 units) and metformin alone or in combination with sulphonylurea/glinides. Basal insulin and sulphonylurea/glinides were discontinued at randomisation. The starting dose of Xultophy® and insulin degludec was 16 units (16 units insulin degludec/0.6 mg liraglutide) and 16 units once daily, respectively, and the dose was titrated in the same way for both twice weekly according to Table **8** above. Patients could not increase their dose by more than 4 units per week and the maximum allowed dose was 50 units for Xultophy® and 50 units for insulin degludec. The targeted fasting plasma glucose goal was achieved in 24.0% of patients randomized to insulin degludec and 31.6% of the patients randomized to Xultophy® at 26 weeks. The primary endpoint, change in HbA1c, was tested for superiority of Xultophy® compared to insulin degludec.

Treatment with Xultophy® resulted in a statistically significant reduction in HbA1c at 26 weeks from baseline compared to insulin degludec (Table 14). 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 comparable between treatment groups. The mean final dose of Xultophy® and insulin degludec was 45 units (for Xultophy® 45 units insulin degludec/1.6 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 insulin degludec dosage can be different than that used in the trial.

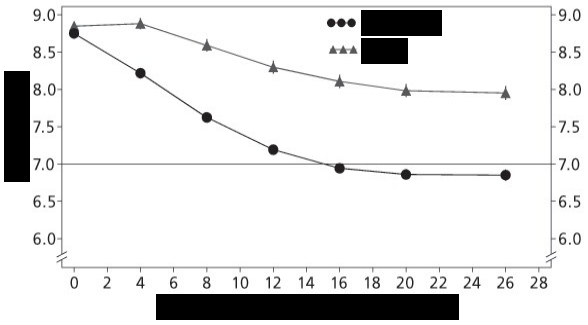
Table 14: Results of a 26 week trial with Xultophy® in patients with type 2 diabetes mellitus inadequately controlled on basal insulin therapies (Trial 3912, DUAL II)

	Previous treatment with basal insulin	
	Xultophy®	**Insulin degludec** Maximum dose 50 units
N	199	199
HbA_{1c} (%) Baseline→End of trial LS mean change# *Estimated difference [95% CI]#* *Superiority p-value*	 8.7→6.9 -1.96	 8.8→8.0 -0.97 *-0.99A[-1.20; -0.78]* p<0.001
Patients achieving HbA_{1c} <7%##	57.3%	22.6%
FPG (mmol/L) Baseline→End of trial LS mean change#	 9.7→6.2 -3.52	 9.6→7.0 -2.93

A Confirmed superiority of Xultophy® vs Insulin Degludec. 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 comparable between treatment groups. The mean final dose of Xultophy and insulin degludec was 45 units (for Xultophy 45 units insulin degludec/1.6 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.

Estimated using an ANCOVA with treatment, country, and previous antidiabetic treatment as fixed factors and baseline response as covariate. Multiple imputation modelled "jump to reference" 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® arm and 13.1% in the insulin degludec arm for whom HbA1c data was missing at week 26.



IDegLira=Xultophy®, IDeg=insulin degludec

Figure 6: Mean HbA1c (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on basal insulin (Trial 3912, DUAL II)

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® 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 randomized 9,340 patients with inadequately controlled type 2 diabetes and with cardiovascular disease to either liraglutide 1.8 mg or placebo. Each was administered subcutaneously once daily, in addition to standard of care treatments for type 2 diabetes mellitus and cardiovascular disease, 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 8% Black; 12% of the population was Hispanic or Latino. The mean duration of type 2 diabetes was 13 years, the mean HbA_{1c} was 8.7% and the mean BMI was 33 kg/m^2; the mean eGFR at baseline was 79 mL/min/1.73 m^2.

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 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 MACE endpoints was 1302 (608 [13.0%] with liraglutide 1.8 mg and 694 [14.9%] with placebo).

Tresiba® (insulin degludec injection)
The DEVOTE trial randomized 7,637 patients with inadequately controlled type 2 diabetes mellitus and with cardiovascular disease to either insulin degludec or insulin glargine U-100. Each was administered subcutaneously once-daily, in addition to standard of care treatments for type 2 diabetes mellitus and cardiovascular disease, 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 (85% 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 HbA_{1c} was 8.4% and the mean BMI was 33.6 kg/m^2. The baseline mean eGFR was 68 mL/min/1.73m^2.

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).

16 NON-CLINICAL TOXICOLOGY

Insulin degludec/liraglutide

The non-clinical development programme for insulin degludec/liraglutide included a pivotal 90-day toxicity study in a single relevant species (Wistar rats) using a combination product with the same fixed-ratio as the clinical formulation. Local tolerance was assessed in rabbits.

Non-clinical safety data reveal no additional safety concern for humans based on the 90-day toxicity study conducted in rats subcutaneously administered insulin degludec/liraglutide daily. No novel toxicity was observed with the fixed ratio combination test article. Effects observed were attributed to the pharmacological effects of insulin degludec or liraglutide previously observed in rats (e.g., decrease in plasma glucose concentration and decrease in body weight, respectively, compared to the control). The NOAEL was determined to be 20 nmol insulin degludec/32 nmol liraglutide per kg body weight per day, the highest dose tested (2.1 times the estimated human AUC for insulin degludec and 3.3 times that for liraglutide). The local tissue reactions observed following a single subcutaneous, intramuscular, or intravenous injection in rabbits were attributed to the injection procedure or the vehicle.

No studies have been conducted with the insulin degludec/liraglutide combination to evaluate carcinogenesis, genotoxicity, or developmental and reproductive toxicity. 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, rats were dosed subcutaneously with insulin degludec at 3.3, 6.7, and 10 U/kg/day, resulting in 5 times the human exposure (AUC) when compared to a human subcutaneous dose of 0.75 U/kg/day. Human insulin was dosed at 6.7 U/kg/day as a comparator. No treatment-related increases in incidences of hyperplasia or in benign or malignant tumors were recorded in female mammary glands from rats dosed with insulin degludec and no treatment-related changes in the female mammary gland cell proliferation were observed. Overall, 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 exposed animals.

Genotoxicity testing of insulin degludec was not performed.

Insulin degludec consists of desB30 human insulin, glutamate, and 1, 16-hexadecanedioic acid. None of the individual components possess mutagenic potential.

In developmental toxicity studies, female rats were subcutaneously administered insulin degludec and human insulin before mating and throughout pregnancy until weaning, while rabbits were exposed during organogenesis. The effect of insulin degludec was consistent with those observed with human insulin as both resulted in pre- and post-implantation losses and skeletal malformations and variations in rats at an insulin degludec dose of 21 U/kg/day (approximately 5 times the human exposure [AUC] at a human subcutaneous dose of 0.75 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure [AUC]). The effects were probably secondary to maternal hypoglycemia, as similar effects were seen after human insulin-induced hypoglycemia in non-diabetic animals.

In a combined fertility and embryo-fetal developmental study in rats, subcutaneous administration of insulin degludec (up to 21 U/kg/day; approximately 5 times the human exposure [AUC]) had no effect on mating performance or fertility in either males or females.

Liraglutide

A 104-week carcinogenicity study was conducted in male and female mice at doses of 0.03, 0.2, 1.0, and 3.0 mg/kg/day administered by subcutaneous bolus injection. Systemic exposures at the 0.03, 0.2, 1, and 3 mg/kg/day doses were 0.2, 1.8, 10.0, and 45.0 times the human exposure, respectively, at the maximum recommended human dose (MRHD) of 1.8 mg/day based on plasma AUC_{0-24} comparison. Treatment resulted in an increased incidence of focal C-cell hyperplasia for males and females dosed at 1.0 and 3.0 mg/kg/day and for females dosed at 0.2 mg/kg/day. Incidence rates of focal C-cell hyperplasia for the 0, 0.03, 0.2, 1.0, and 3.0 mg/kg/day groups, respectively, were 0%, 0%, 1.5%, 16.4%, and 38.0% for males and 0%, 0%, 10.4%, 10.5%, and 33.3% for females. There was also a dose-related increase in benign thyroid C-cell adenomas in the 1.0 and the 3.0 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or in the 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3.0 mg/kg/day group. Thyroid C-cell tumours are rare findings during carcinogenicity testing in mice. In addition, there was a treatment-related increase in fibrosarcomas on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation of liraglutide (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL). The NOAEL for this study is 0.03 mg/kg/day.

A 104-week carcinogenicity study was conducted in male and female rats at doses of 0.075, 0.25 and 0.75 mg/kg/day administered by bolus subcutaneous injection with exposures 0.5, 2.2, and 7.6 times the human exposure level, respectively, at the MRHD based on plasma AUC_{0-24} comparison. There was a treatment-related increase in the incidence and severity of focal C-cell hyperplasia in the 0.25 and 0.75 mg/kg/day groups. Incidence rates of focal C-cell hyperplasia for the 0, 0.075, 0.25, and 0.75 mg/kg/day groups, respectively, were 22%, 29%, 40%, and 48% for males and 28%, 29%, 55%, and 48% for females. In addition, there was a treatment-related increase in benign thyroid C-cell adenomas noted for males in the 0.25 and 0.75 mg/kg/day groups and for females in all treated groups. Incidence rates of thyroid C-cell adenomas for the 0, 0.075, 0.25, and 0.75 mg/kg/day groups, respectively, were 12%, 16%, 42%, and 46% for males and 10%, 27%, 33%, and 56% for females. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups and in females at 0.25 and 0.75 mg/kg/day. Incidences rates of thyroid C-cell carcinomas for the 0, 0.075, 0.25, and 0.75 mg/kg/day groups, respectively, were 2%, 8%, 6%, and 14% in males and 0%, 0%, 4%, and 6% in females. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Based on liraglutide-related adverse findings at all doses tested, a NOAEL could not be determined for this study.

The human relevance of thyroid C-cell tumors observed in rats and mice is unknown and could not be determined based on the results of the nonclinical studies (refer to WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis; Boxed Warnings and Precautions).

Liraglutide was not mutagenic or clastogenic with or without metabolic activation in the following tests: Ames test, human peripheral blood lymphocyte chromosome aberration test, and in vivo micronucleus test in the rat.

In rat fertility and embryo-fetal developmental study, rats were administered liraglutide subcutaneously at doses of 0.1, 0.25 and 1.0 mg/kg/day. Males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility were observed up to the highest dose levels tested, which represented a systemic exposure 11 times the human exposure at the MRHD based on plasma AUC. Body weight gain and food intake were transiently reduced at all dose levels. At 1.0 mg/kg/day, there was an increased incidence of early embryonic death and an increase in the number of fetuses and litters with minimally kinked ribs. The fetal NOAEL/NOEL was therefore considered to be 0.25 mg/kg/day.

In a rabbit developmental study, pregnant females were administered liraglutide subcutaneously at doses of 0.01, 0.025, and 0.05 mg/kg/day from gestation day 6 through day 18 inclusive. The estimated systemic exposures were less than the human exposure at the MRHD at all doses, based on plasma AUC. Fetal weight was decreased and the incidence of total major fetal abnormalities was increased at all dose levels tested. Single cases of microphthalmia were noted at all dose levels. Since microphthalmia is a very rare malformation, and was not observed in the control group or in any of the historical control groups, this finding is considered to be related to treatment. In addition, there was an increase in the fetal incidence of connected parietals in the high dose group and a single case of split sternum in the 0.025 and 0.05 mg/kg/day groups, which could not be ruled out as unrelated to treatment. Minor abnormalities considered to be treatment-related were an increase in the incidence of jugal(s) connected/fused to maxilla at all dose levels and an increase in the incidence of bilobed/bifurcated gallbladder at 0.025 and 0.50 mg/kg/day. The noted findings exceeded the incidence noted in the concurrent and historical controls. Based on these data, a NOEL/NOAEL for embryo/fetal toxicity could not be determined. Liraglutide is considered to be a possible teratogen in rabbits due to the increased incidence of major abnormalities noted at all dose levels tested.

In a pre- and post-natal study, pregnant female rats were administered 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 the human exposure, respectively, based on plasma AUC. Reduced body weight gain/weight loss and decreased food consumption were observed in all treated groups, evident primarily during the first 3 days of dosing. At 1.0 mg/kg/day, following the initial weight loss, the difference in absolute weight when compared to controls was not recovered by the end of gestation. Lesser effects were noted at the lower dose levels. In addition, decreased weight gain was evident in F0 females that had been treated with 1.0 mg/kg/day between Days 1 and 14 of lactation. Litter size and survival were similar in all groups, but decreased weight gain was evident in the F1 pups prior to weaning at all dose levels. The reduced body weight of F1 pups persisted in the post-weaning period, but only at 1.0 mg/kg/day was there also a reduction in weight gain, which was noted for males, as well as for females during the lactation period. There were no apparent treatment-related effects on the development, behaviour, physiology, or reproductive function of the F1 animals, except for a slight reduction in body weights of F2 pups at 1.0 mg/kg/day.

17 SUPPORTING PRODUCT MONOGRAPHS

Victoza® (Solution, 6 mg/mL), submission control 200821, Product Monograph, Novo Nordisk Canada Inc. (NOV, 17, 2017)

Tresiba® (Solution, 100 U/mL, 200 U/mL), submission control 216199, Product Monograph, Novo Nordisk Canada Inc. (APR, 17, 2019)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrXULTOPHY®
insulin degludec+liraglutide injection
(Zul-to-fye)

Read this carefully before you start taking **Xultophy®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Xultophy®**.

Serious Warnings and Precautions

- Low blood sugar is the most common adverse effect of insulin, including Xultophy®.
- If low blood sugar or high blood sugar reactions are not treated they can result in the loss of consciousness, coma or death.
- Blood sugar levels should be monitored for all patients with diabetes.
- Any change of insulin should be made cautiously and only under medical supervision. This may result in dosage adjustment.
- Never inject your insulin directly into a vein.
- Never use Xultophy® in insulin infusion pumps.
- Only use Xultophy® if it appears water clear or colourless.
- Xultophy® must not be mixed with any other insulin.
- Possible Risk of thyroid tumours, including cancer
- As part of drug testing, liraglutide, one of the ingredients in Xultophy® was given to rats and mice in long term studies. In these studies, liraglutide caused both rats and mice to develop medullary thyroid tumours, some of which were cancer. It is not known if liraglutide will cause thyroid tumours or a type of thyroid cancer called medullary thyroid cancer in people. Medullary thyroid cancer in humans is rare; however it is serious and potentially fatal.
- If you develop tumours of the thyroid, it may have to be surgically removed. You should discuss any safety concerns you have about the use of liraglutide with your doctor.

What is Xultophy® used for?

Xultophy® is used, in combination with oral medicines for diabetes, to improve blood glucose (sugar) levels in adult patients with type 2 diabetes mellitus. You have diabetes because your body:

- Does not make enough insulin to control the level of sugar in your blood, or
- Is not able to use the insulin properly.

Xultophy® should not be used in type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM) or for the treatment of diabetic ketoacidosis (increased ketones in the blood or urine).

How does Xultophy® work?

Xultophy® contains two active substances that help your body control your blood sugar:

- Insulin degludec – a long-acting basal insulin which lowers your blood sugar levels, and
- Liraglutide – a ‘GLP-1 receptor agonist’ that helps your body make more insulin during

meals and lowers the amount of sugar made by your body.

Xultophy® and oral medicines for diabetes
Xultophy® is used with oral medicines for diabetes (such as metformin, pioglitazone, sulfonylurea and sodium-glucose cotransporter 2 inhibitors (SGLT2i) medicines). It is prescribed when these medicines (used alone or with GLP-1 treatment or with basal insulin) are not enough to control your blood sugar levels.

If you use GLP-1 treatment
You should stop your GLP-1 treatment prior to starting on Xultophy®.

If you use basal insulin
You should stop your basal insulin treatment prior to starting on Xultophy®.

What are the ingredients in Xultophy®?
Medicinal ingredients: The active substances are insulin degludec and liraglutide. Each mL of solution contains 100 units of insulin degludec and 3.6 mg liraglutide. Each unused pre-filled pen (3 mL) contains 300 units of insulin degludec and 10.8 mg liraglutide.

Non-medicinal ingredients: glycerol, hydrochloric acid, phenol, sodium hydroxide (for pH adjustment), water for injections and zinc acetate.

Xultophy® comes in the following dosage forms:
Xultophy® is an injection supplied as a sterile, clear, colorless solution in a 3 mL pre-filled, disposable, single-patient use pen injector.

The pre-filled pen can provide from 1 up to 50 units in one injection in increments of one unit.

The pre-filled pen is recommended to be used with NovoFine® or NovoTwist® injection needles up to a length of 8 mm and as thin as 32G.

Do not use Xultophy® if:
- You are allergic to insulin degludec or liraglutide or any of the other ingredients of this medicine. See *'What are the ingredients in Xultophy®'*.
- If you think that your blood sugar is getting too low (this is called "hypoglycemia").
- You or a member of your family has ever had medullary thyroid cancer.
- You have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- You are pregnant or breastfeeding.

As a precautionary measure,
- Always carry a spare Xultophy® and new needles with you, in case of loss or damage.
- Always carry something to show you have diabetes.
- Always carry products containing sugar with you. See the section on '*Low blood sugar (hypoglycemia)*'.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Xultophy®. Talk about any health conditions or problems you may have, including if you:
- Or a member of your family has or has had medullary thyroid carcinoma, or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

- Have a high heart rate (fast pulse).
- Have a condition called heart block.
- Have any heart disease, such as angina, heart rhythm disturbances or congestive heart failure; or if you have ever had a myocardial infarction (heart attack).
- Have or have had problems with your pancreas, kidneys, or liver.
- Are pregnant, or planning a pregnancy or are breastfeeding or plan to breastfeed.
- Have eye problems. Fast improvements in blood sugar control may make diabetic eye problems get worse for a short time. The long-term improvements in blood sugar control may ease the eye problems.
- Have or have had a thyroid disease.
- If you are also taking a sulphonylurea (such as glimepiride or glibenclamide), your doctor may tell you to lower your sulphonylurea dose depending on your blood sugar levels.
- The use of Xultophy® is not recommended in patients with inflammatory bowel disease or delayed gastric emptying (diabetic gastroparesis).
- If you drink alcohol (including wine and beer) your need for insulin may change as your blood sugar level may either rise or fall.
- If you have an infection, fever or have had an operation you may need more insulin than usual.
- If you suffer from diarrhea, vomiting or eat less than usual you may need less insulin than usual.
- If you exercise more than usual or if you want to change your usual diet.
- If you are ill: continue taking your insulin.
- If you go abroad: travelling over time zones may affect your insulin needs and the timing of injections. Consult your doctor if you are planning such travel.
- If you drive or use tools or machines: watch for signs of hypoglycemia. Your ability to concentrate or to react will be less during a hypoglycemic reaction. Please keep this in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). Never drive or use machinery if you feel a hypoglycemic reaction coming on.
- Have type 1 diabetes.
- Have ever had diabetic ketoacidosis (increased ketones in the blood or urine).
- Have gastrointestinal (digestive) problems.

Be especially aware of the following when using Xultophy®:
- Low blood sugar (hypoglycemia) – if your blood sugar is low, follow the advice in *'Low blood sugar (hypoglycemia)'*.
- High blood sugar (hyperglycemia) – if your blood sugar is high, follow the advice in *high blood sugar (hyperglycemia)'*.

If you have a severe stomach ache which does not go away, tell your doctor – this could be a sign of inflamed pancreas (acute pancreatitis).

Dehydration (loss of fluids from the body) can happen if you are feeling or being sick (nausea or vomiting) or have diarrhea – it is important to drink plenty of fluids to stop dehydration.

Skin changes at the injection site
The injection site should be rotated to help prevent changes to the fatty tissue under the skin, such as skin thickening, skin shrinking or lumps under the skin. The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Tell your doctor if you notice any skin

changes at the injection site. Tell your doctor if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Other warnings you should know about:
Before you travel, check with your physician or pharmacist on the availability of Xultophy® in other countries. If possible, bring enough Xultophy® with you on your trip.

Thiazolidinediones (class of oral antidiabetic drugs) used together with insulin may increase risk of edema and heart failure. Inform your doctor as soon as possible if you experience localized swelling (edema) or signs of heart failure such as unusual shortness of breath.

Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disorder.

Always check the pen label before you inject your medicine to ensure that you use the correct pen.

Do not transfer Xultophy® from the pen into a syringe, as the markings on the insulin syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia.

Do not share your Xultophy® pen with another person, even if the needle is changed. Do not reuse or share needles with another person. You may give another person an infection or get an infection from them.

Driving and using machines
Having low or high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is low or high, your ability to concentrate or react might be affected. This could be dangerous to yourself or others. Ask your doctor whether you can drive if:

- You often get low blood sugar.
- You find it hard to recognise low blood sugar.

Children and Adolescents
Do not give this medicine to children or adolescents. There is no experience with Xultophy® in children and adolescents under 18 years old.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
Some medicines affect your blood sugar level – this may mean your Xultophy® dose has to change. Listed below are the most common medicines, which may affect your treatment. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

Your blood sugar level may fall if you take:

- Other medicines for diabetes (tablets or injections);
- Sulphonamides antibiotics (medicines used to treat infections);
- Anabolic steroids (used as testosterone);
- Beta-blockers (used to treat high blood pressure). They may make it harder to recognise the warning signs of low blood sugar (see *'Warning signs of low blood sugar – these may come on suddenly'*);

- Acetylsalicylic acid (and medicines called 'salicylates') – for pain and mild fever;
- Monoamine oxidase inhibitors (MAOI) (used to treat depression);
- Medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide;
- A sulfonylurea medicine (such as glibenclamide or glimepiride). This is because using Xultophy® at the same time may cause your blood sugar to get too low (hypoglycemia);
- Fluoxetine;
- Fibrates (medicine used for lowering high levels of blood fats);
- Medicines used to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates;
- When you first start using these medicines together, your doctor may tell you to lower the dose of the sulfonylurea medicine;
- If you are not sure if the medicines you are taking contain a sulfonylurea, ask your doctor, Diabetes Nurse Educator or pharmacist;
- Octreotide (used for treatment of acromegaly (a rare illness with too much growth hormone).

Your blood sugar level may rise if you take:

- Danazol (medicine acting on ovulation);
- Oral contraceptives (birth control pills);
- Growth hormone – for low levels of growth hormone;
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, albuterol or terbutaline used to treat asthma);
- Diuretics (also called water pills), used to treat high blood pressure or fluid retention;
- Thiazides (used to treat high blood pressure or excessive fluid retention);
- Corticosteroids such as cortisone (used to treat inflammation);
- Isoniazid (used to treat tuberculosis);
- Niacin and phenothiazine;
- Hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), somatotropin, thyroid hormones, glucagon;
- Protease inhibitors (used to treat HIV infection);
- Medicines used to treat mental health problems, such as: olanzapine, clozapine;

Pioglitazone – tablets used for the treatment of type 2 diabetes mellitus. Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke, who were treated with pioglitazone and insulin, experienced the development of heart failure. Inform your doctor straight away if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Warfarin or other blood thinners – medicines used to prevent clotting of the blood. Tell your doctor if you are taking warfarin or other blood thinners as you might need to have blood tests more often to measure how thick your blood is (called 'International Normalised Ratio' or INR test).

Xultophy® with alcohol

- If you drink alcohol, your need for Xultophy® may change. Your blood sugar level may either rise or fall. You should therefore monitor your blood sugar level more often than usual.

The following may interact with Xultophy®:
The following list includes some, but not all, of the drugs that may increase the risk of heart rhythm problems while receiving Xultophy®. You should check with your doctor or pharmacist before taking any other medication with Xultophy®:

- Drugs to treat hypertension.
- Drugs to treat heart failure.
- Drugs to treat HIV infection.
- Drugs to treat attention deficit-hyperactivity disorder.
- Drugs to suppress appetite/cause weight loss.
- Decongestants.

Drugs to treat asthma.

How to take Xultophy®:
Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Your doctor will tell you:

- How much Xultophy® you will need each day.
- When to check your blood sugar level.
- How to adjust the dose.

How to handle Xultophy®

- Xultophy® is a pre-filled dial-a-dose pen.
- Xultophy® is administered as 'units'. The dose counter on the pen shows the number of units.
- One unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide.
- The maximum daily dose of Xultophy® is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide).
- Carefully read the '*Instructions For Use*' and use the pen as described.
- Always check the pen label before you inject your medicine to ensure that you use the correct pen.

How to inject

- Before you use Xultophy® for the first time, your doctor or nurse will show you how to inject.
- Xultophy® is given as an injection under the skin (subcutaneously). Do not inject it into a vein or muscle.
- The best places to inject are the front of your thighs, upper arms or the front of your waist (abdomen).
- Change the place within the area where you inject each day to reduce the risk of developing lumps and skin pitting (see '*What are possible side effects from using Xultophy®?*').
- Detailed instructions for use are included in the '*Instructions For Use*'.

Do not use Xultophy®

- If the pen is damaged or has not been stored correctly (see '*Storage*').
- If the liquid you can see through the pen window does not look clear and colourless.

Use in elderly patients (65 years old or over)
Xultophy® can be used in elderly patients but if you are elderly you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

If you have kidney or liver problems
If you have kidney or liver problems you may need to check your blood sugar level more often. Talk to your doctor about changes in your dose.

If you stop using Xultophy®
Do not stop using Xultophy® without talking to your doctor. If you stop using Xultophy® this could lead to a very high blood sugar level, see the advice in '*High blood sugar (hyperglycemia)*'.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Usual dose:
Dosing time
- Use Xultophy® once each day, preferably at the same time every day. Choose a time of the day that works best for you.
- You do not have to use Xultophy® with a meal.
- Always follow your doctor's advice for dose and dose adjustment.
- If you want to change your usual diet, check with your doctor, pharmacist or nurse first as a change in diet may alter your need for Xultophy®.

Overdose:
The maximum daily dose of Xultophy® is 50 units (50 units insulin degludec and 1.8 mg liraglutide). The dose counter on the pen shows the number of units.

If you use more Xultophy® than you should, your blood sugar may get low (hypoglycemia) or you may feel or be sick (nausea or vomiting). If your blood sugar gets low, see the advice in '*Low blood sugar (hypoglycemia*)'.

If you think you have taken too much Xultophy®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of Xultophy®, 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®, call your healthcare professional for further instructions about taking Xultophy® at the right dose and to help lower your chance of having an upset stomach.

What are possible side effects from using Xultophy®**?**
Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very common (may affect more than 1 in 10 people)

Too low blood sugar (Hypoglycemia): If your blood sugar level gets low you may pass out (become unconscious). Serious hypoglycemia may cause brain damage and may be life-threatening. If you have signs of low blood sugar, take actions to increase your blood sugar level straight away. See advice in '*Low blood sugar (hypoglycemia*)'.

Other side effects include:

Common (may affect up to 1 in 10 people)
- Lower appetite, feeling or being sick (nausea or vomiting), diarrhea, constipation, indigestion (dyspepsia), inflamed lining of the stomach (gastritis), stomach ache, heartburn, or bloating – these usually go away after a few days or weeks.
- Injection site reactions. The signs may include bruising, bleeding, pain, redness, hives, swelling or itching – these usually go away after a few days. See your doctor if they do not disappear after a few weeks. Stop using Xultophy® and see a doctor straight away if they become serious.
- Increase of pancreatic enzymes, such as lipase and amylase.

Uncommon (may affect up to 1 in 100 people)
- Hives.
- Allergic reactions (hypersensitivity) such as rash, itching and swelling of the face.
- Dehydration (loss of fluid from the body) – it is important to drink plenty of fluids to stop dehydration.
- Belching (eructation) and wind (flatulence).
- Rash.
- Itching.
- Skin changes where you give the injection ('lipodystrophy') – the fatty tissue under the skin may shrink ('lipoatrophy') or get thicker ('lipohypertrophy'). Changing the place where you inject each time may reduce the risk of these skin changes. If you notice these skin changes, tell your doctor or nurse. If you keep injecting in the same place, these changes can become more severe and affect the amount of medicine your body gets from the pen.
- Increased heart rate.
- Tiredness.
- Gallstones.
- Inflamed gallbladder.

Not known (frequency cannot be estimated from the available data)
- Inflamed pancreas (pancreatitis).
- Swelling of arms or legs (peripheral oedema) – when you first start using your medicine, your body may keep more water than it should. This causes swelling around your ankles and other joints. This is usually only short-lasting.
- Serious allergic reaction (anaphylactic reaction) (not known: frequency cannot be estimated from the available data).
- Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy, shrunken or thickened area. Change the injection site with each injection to help prevent these skin changes.

If you have a serious allergic reaction to any of the ingredients in Xultophy®, stop using Xultophy® and see a doctor straight away. The signs of a serious allergic reaction may include:
- Local reactions (e.g. rash, redness, and itching) spread to other parts of your body.
- You suddenly feel unwell with sweating.
- You have difficulty breathing.
- You get a fast heart beat or feel dizzy.

General effects from diabetes treatment

Low blood sugar (hypoglycemia)

Low blood sugar may happen if you
- Drink alcohol
- Exercise more than usual
- Eat too little or miss a meal
- Use too much Xultophy®

Warning signs of low blood sugar – these may come on suddenly
Headache, slurred speech, fast heart beat, cold sweat, cool pale skin, feeling sick (nausea), feeling very hungry, shaking, feeling nervous or worried, unusually tired, weak and sleepy or confused, difficulty concentrating, short-lasting changes in your sight.

What to do if you get low blood sugar
Eat glucose tablets or another high sugar snack – like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once. This is because improvement in your blood sugar may not happen straight away.
- Wait until the signs of low blood sugar have gone or when your blood sugar level has settled. Then carry on with your medicine as usual.

What others need to do if you pass out
Tell everyone you spend time with that you have diabetes. Tell them what could happen if your blood sugar gets low, including the risk of passing out.

Let them know that if you pass out, they must:
- Turn you on your side
- Get medical help straight away
- Not give you any food or drink – because you may choke

You may recover more quickly from passing out with an injection of glucagon. This can only be given by someone who knows how to use it.
- If you are given glucagon you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to a glucagon injection, you will have to be treated in a hospital.
- If severe low blood sugar is not treated over time, it can cause brain damage. This can be short- or long-lasting. It may even cause death.

Talk to your doctor if
- Your blood sugar got so low that you passed out
- You have had an injection of glucagon
- You have had low blood sugar a few times recently

This is because the dosing of your Xultophy® injections, food or exercise may need to be changed.

High blood sugar (hyperglycemia)

High blood sugar may happen if you

- Drink alcohol
- Exercise less than usual
- Eat more than usual
- Get an infection or a fever
- Have not used enough Xultophy®, keep using less Xultophy® than you need, forget to use Xultophy® or stop using Xultophy® without talking to your doctor

Warning signs of high blood sugar – these normally appear gradually
Flushed, dry skin, feeling sleepy or tired, dry mouth, fruity (acetone) breath, urinating more often, feeling thirsty, losing your appetite, feeling or being sick (nausea or vomiting).
These may be signs of a very serious condition called 'ketoacidosis'. This is a build-up of acid in the blood because the body is breaking down fat instead of sugar. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get high blood sugar

- Test your blood sugar level
- Test your urine for ketones
- Get medical help straight away

These are not all the possible side effects you may feel when taking Xultophy®. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Hypoglycemia (low blood sugar) symptoms: feeling confused, fits and passing out.		√	√
Gastrointestinal disorders such as Nausea, vomiting, dyspepsia and constipation		√	
Reaction at injection site		√	
UNCOMMON Increased Heart Rate, chest pain or symptoms of possible heart rhythm disturbance/dizziness, palpitations, fainting or seizures		√	√
Changes under the skin where you use the injection (lipodystrophy)		√	
UNKNOWN Severe form of allergic reaction (anaphylactic reaction) with symptoms of breathing problems, swelling of throat and face, and fast heart beat. You should seek immediate medical attention		√	√
Pancreatitis / persistent, severe abdominal pain (stomach area) which might reach through your back, as well as nausea with or without vomiting		√	√
Low potassium in your blood (hypokalemia)		√	√
Kidney problems (kidney failure). In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.		√	√
Thyroid tumour / lump in the neck, difficulty in swallowing difficulty in breathing or persistent hoarseness		√	
Cutaneous Amyloidosis: lumps under skin		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening
Store in a refrigerator (2°C to 8°C). Keep away from the freezing element. Do not freeze.

During use
Do not freeze. You can carry Xultophy® with you and keep it at room temperature (no more than 30°C) or in a refrigerator (2°C to 8°C) for up to 21 days. The product should be thrown away 21 days after first opening.

Always keep the cap on the pre-filled pen when you are not using it in order to protect it from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about Xultophy®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the Novo Nordisk website (www.novonordisk.ca), or by calling Novo Nordisk Canada Inc., at 1-800-465-4334.

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18 INSTRUCTIONS FOR USE

Instructions on how to use Xultophy® 100 units/mL + 3.6 mg/mL solution for injection

Please read these instructions carefully before using your Xultophy® pre-filled pen.
Do not use the pen without proper training from your doctor or nurse.

Start by checking your pen to **make sure that it contains Xultophy® 100 units/mL + 3.6 mg/mL,** then look at the illustrations below to get to know the different parts of your pen and needle.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Xultophy® pre-filled pen.

Xultophy® is a medicine that contains insulin degludec and liraglutide. Xultophy® is administered as 'units'. One unit contains 1 unit insulin degludec + 0.036 mg liraglutide.

Your pen is a pre-filled dial-a-dose pen. It contains 3 mL of Xultophy® solution. It delivers doses from:
– 1 unit
– to a **maximum of 50 units** (50 units insulin degludec + 1.8 mg liraglutide)

Your pen delivers doses in increments of 1 unit.
Do not do any conversion of your dose. The units dialed equal the number shown in the dose counter.

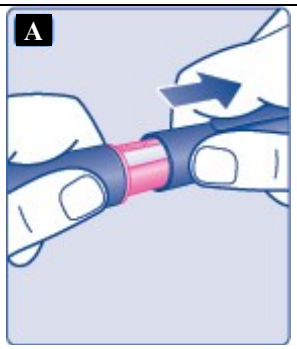
Your pen is recommended to be used with NovoTwist® or NovoFine® disposable needles up to a length of 8 mm and as thin as 32G. Needles are not included in the pack.

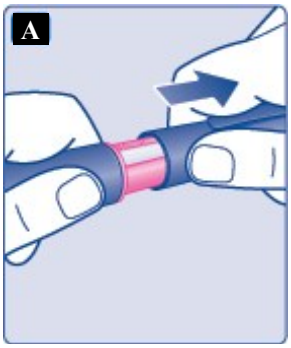
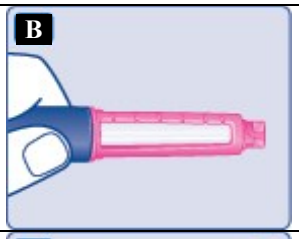
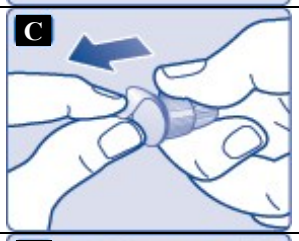
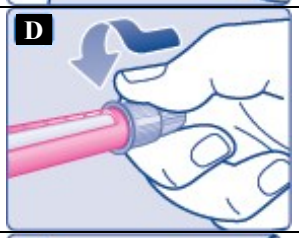
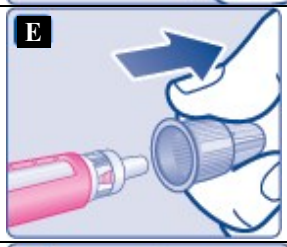
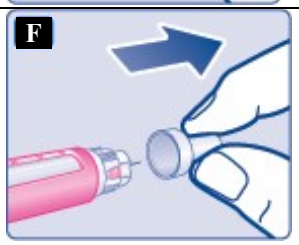
⚠ Important information
Pay special attention to these notes as they are important for safe use of the pen.

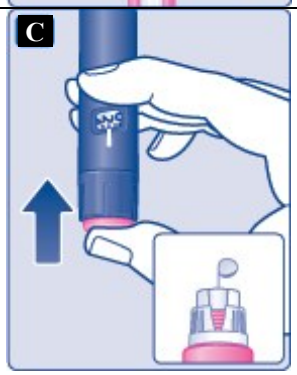
1 Prepare your pen with a new needle

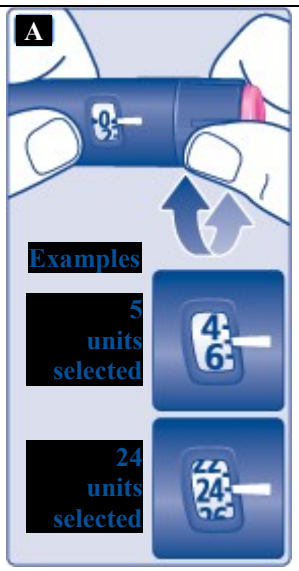
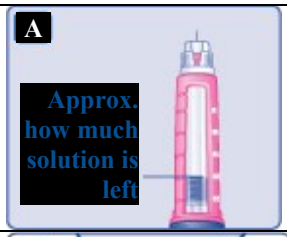
- **Check the name and coloured label** of your pen, to make sure that it contains Xultophy®.
  This is especially important if you take more than one type of injectable medicine. Taking the wrong medicine could be harmful to your health.

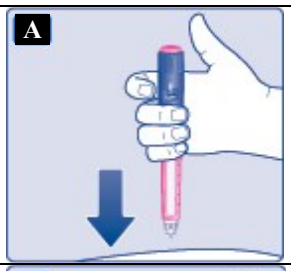
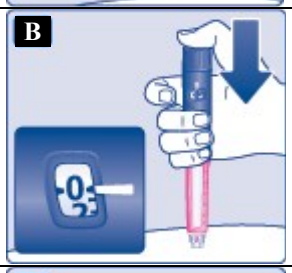
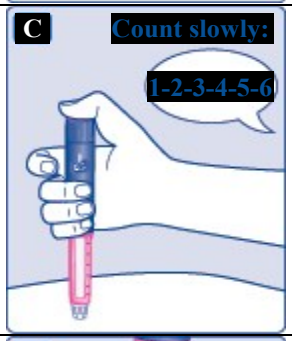
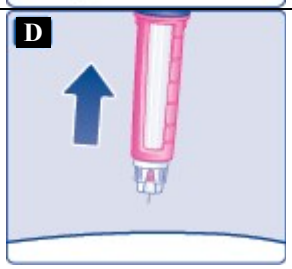
- **Pull off the pen cap.**

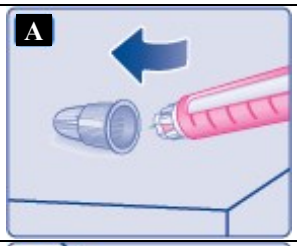
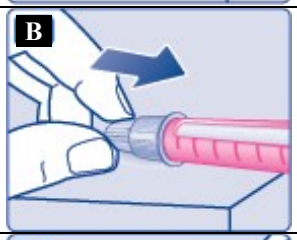
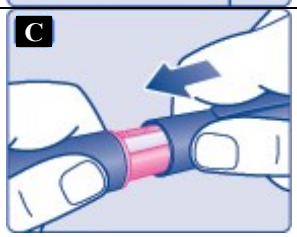


	
• **Check that the solution in your pen is clear** and colourless. Look through the pen window. If the solution looks cloudy, do not use the pen.	
• **Take a new needle,** and tear off the paper tab.	
• **Push the needle straight onto the pen. Turn until it is on tight.**	
• **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.	
• **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle. A drop of solution may appear at the needle tip. This is normal, but you must still check the flow. **Do not attach a new needle** to your pen until you are ready to take your injection. ⚠ **Always use a new needle for each injection.**	

This may prevent blocked needles, contamination, infection and inaccurate dosing. ⚠ **Never use a bent or damaged needle.**	
2 Check the flow • Turn the dose selector to **select 2 units.** Make sure the dose counter shows 2. • The dose counter and the dose pointer show how many units of Xultophy® you select.	
• 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.	
• **Press and hold in the dose button** until the dose counter returns to 0. The 0 must line up with the dose pointer. A drop of solution should appear at the needle tip. A small drop may remain at the needle tip, but it will not be injected. **If no drop appears,** repeat steps **2A** to **2C** up to 6 times. If there is still no drop, change the needle and repeat steps **2A** to **2C** once more. **If a drop of solution still does not appear,** dispose of the pen and use a new one. ⚠ **Always make sure that a drop appears** at the needle tip before you inject. This makes sure that the solution flows. If no drop appears, you will **not** inject any medicine, even though the dose counter may move. **This may indicate a blocked or damaged needle.** ⚠ **It is important always to check the flow before you inject.** If you do not check the flow, you may get too little medicine, or no medicine at all. This may lead to high blood sugar level.	

3 Select your dose • **Turn the dose selector to select the dose you need.** The dose counter shows the dose in units. If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose. The pen can dial up to a maximum of 50 units. The dose selector changes the number of units. Only the dose counter and dose pointer will show how many units you select per dose. You can select up to 50 units per dose. When your pen contains less than 50 units, the dose counter stops at the number of units left. The dose selector clicks differently when turned forwards, backwards or past the number of units left. Do not count the pen clicks. ⚠ **Always use the dose counter and the dose pointer to see how many units you have selected before injecting the medicine.** Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get high or low. Do not use the pen scale, it only shows approximately how much solution is left in your pen.	
How much solution is left? • The **pen scale** shows you **approximately** how much solution is left in your pen.	
• **To see precisely how much solution is left,** use the dose counter: Turn the dose selector until the **dose counter stops.** If it shows 50, **at least 50** units are left in your pen. If it shows **less than 50,** the number shown is the number of units left in your pen. If you need more medicine than what is left in your pen, you can split your dose between two pens. ⚠ **Be very careful to calculate correctly if splitting your dose.** If in doubt, take the full dose with a new pen. If you split the dose wrongly, you will inject too little or too much medicine. This may make your blood sugar level high or low.	

4 Inject your dose • **Insert the needle into your skin** as your doctor or nurse has shown you. • **Make sure you can see the dose counter.** Do not cover it with your fingers. This could interrupt the injection.	
• **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.	
• **Keep the needle in your skin after** the dose counter has returned to 0 and **count slowly to 6.** • If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered, and you should increase the frequency of checking your blood sugar level.	
• **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area. You may see a drop of solution at the needle tip after injecting. This is normal and does not affect your dose. ⚠ **Always watch the dose counter to know how many units you inject.** Hold the dose button down until the dose counter shows 0. If the dose counter does not return to 0, the full dose has not been delivered, which may lead to high blood sugar level. **How to identify a blocked or damaged needle?** • If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle. • In this case - you have **not** received **any** medicine - even though the dose counter has moved from the original dose that you have set. **How to handle a blocked needle?** Change the needle as described in section 5 and repeat all steps starting with section 1: Prepare your pen with a new needle. Make sure you select the full dose you need.	

Never touch the dose counter when you inject. This can interrupt the injection.	
5 After your injection • **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer cap.	
• Once the needle is covered, **carefully push the outer needle cap completely on.** • **Unscrew the needle** and dispose of it carefully as instructed by your doctor or nurse.	
• **Put the pen cap on** your pen after each use to protect the solution from light. **Always dispose of the needle after each injection** to ensure the use of a sharp needle and prevent blocked needles. If the needle is blocked, you will **not** inject any medicine. When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities. ⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle. ⚠ **Always remove the needle from your pen after each injection.** This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.	
⚠ **Further important information** • **Always keep an extra pen and new needles**, in case of loss or damage. • Always keep your pen and needles **out of sight and reach of others,** especially children. • **Never share your pen** with other people. Your medicine might be harmful to their health. • **Never share your needles** with other people. It might lead to cross-infection. • Caregivers must **be very careful when handling used needles** – to prevent needle injury and cross-infection.	
Caring for your pen • **Do not leave the pen in a car** or other place where it can get too hot or too cold. • **Do not store your pen at temperatures above 30°C.** • **Do not expose your pen to dust, dirt or liquid.** • **Do not wash, soak or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth. • **Do not drop your pen** or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the flow before you inject. • **Do not try to refill your pen.** Once empty, it must be disposed of.	

- **Do not try to repair your pen** or pull it apart.