**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Xultophy 100 units/mL + 3.6 mg/mL solution for injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 100 units insulin degludec* and 3.6 mg liraglutide*.

*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

One pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 10.8 mg liraglutide.

One dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, isotonic solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).

### 4.2 Posology and method of administration

Posology

Xultophy is given once daily by subcutaneous administration. Xultophy can be administered at any time of the day, 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 glycaemic control via dose adjustment based on fasting plasma glucose.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule. A minimum of 8 hours between injections should always be ensured. This also applies when administration at the same time of the day is not possible.

Xultophy is administered as dose steps. One dose step contains 1 unit of insulin degludec and

0.036 mg of liraglutide. The pre-filled pen can provide from 1 up to 50 dose steps in one injection in increments of one dose step. The maximum daily dose of Xultophy is 50 dose steps (50 units insulin degludec and 1.8 mg liraglutide). The dose counter on the pen shows the number of dose steps.

*Add-on to oral glucose-lowering medicinal products*
The recommended starting dose of Xultophy is 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide).

Xultophy can be added to existing oral anti-diabetic treatment. When Xultophy is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered (see section 4.4).

*Transfer from GLP-1 receptor agonist*
Therapy with GLP-1 receptor agonists should be discontinued prior to initiation of Xultophy. When transferring from a GLP-1 receptor agonist, the recommended starting dose of Xultophy is 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) (see section 5.1). The recommended starting dose should not be exceeded. If transferring from a long-acting GLP-1 receptor agonist (e.g. once-weekly dosing), the prolonged action should be considered. Treatment with Xultophy should be initiated at the moment the next dose of the long-acting GLP-1 receptor agonist would have been taken. Close glucose monitoring is recommended during the transfer and in the following weeks.

*Transfer from basal insulin*
Therapy with basal insulin should be discontinued prior to initiation of Xultophy. When transferring from basal insulin therapy, the recommended starting dose of Xultophy is 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) (see section 4.4 and 5.1). The recommended starting dose should not be exceeded. Close glucose monitoring is recommended during the transfer and in the following weeks.

*Special populations*

*Elderly patients (≥65 years old)*
Xultophy can be used in elderly patients. Glucose monitoring is to be intensified and the dose adjusted on an individual basis. The therapeutic experience in patients ≥75 years of age is limited.

*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 section 5.2).

*Hepatic impairment*
Xultophy can be used in patients with mild or moderate hepatic impairment. Glucose monitoring is to be intensified and the dose adjusted on an individual basis.
Due to the liraglutide component, Xultophy is not recommended for use in patients with severe hepatic impairment (see section 5.2).

*Paediatric population*
There is no relevant use of Xultophy in the paediatric population.

Method of administration

Xultophy is for subcutaneous use only. Xultophy must not be administered intravenously or intramuscularly.

Xultophy is administered subcutaneously by injection in the thigh, the upper arm or the abdomen. Injection sites are always to be rotated within the same region in order to reduce the risk of lipodystrophy. For further instructions on administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to either or both active substances or to any of the excipients listed in section 6.1.
Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2

## 4.4 Special warnings and precautions for use

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

Hypoglycaemia

Hypoglycaemia may occur if the dose of Xultophy is higher than required. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In combination with sulfonylurea, the risk of hypoglycaemia may be lowered by a reduction in the dose of sulfonylurea. 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 of hypoglycaemia and must be advised accordingly. Usual warning symptoms (see section 4.8) of hypoglycaemia may disappear in patients with long-standing diabetes. The prolonged effect of Xultophy may delay recovery from hypoglycaemia.

Hyperglycaemia

Inadequate dosing and/or discontinuation of anti-diabetic treatment may lead to hyperglycaemia and potentially to hyperosmolar coma. In case of discontinuation of Xultophy, ensure that instruction for initiation of alternative anti-diabetic medication is followed. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased requirement for anti-diabetic treatment. Usually, the first symptoms of hyperglycaemia 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 hyperglycaemia. Untreated hyperglycaemic events eventually lead to hyperosmolar coma/diabetic ketoacidosis, which is potentially lethal.

Combination of pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin medicinal products, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of pioglitazone and Xultophy is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

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.

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 hypoglycaemia. 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.

Acute pancreatitis

Use of GLP-1 receptor agonists including liraglutide, a component of Xultophy, has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis. 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.

Thyroid adverse events

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, a component of Xultophy, in particular in patients with pre-existing thyroid disease, and Xultophy should therefore be used with caution in these patients.

Inflammatory bowel disease and diabetic gastroparesis

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

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.

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.

Populations not studied

Transfer to Xultophy from doses of basal insulin <20 and >50 units has not been studied.

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

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.

Excipients

Xultophy contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially ‘sodium-free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Interaction studies with Xultophy have not been performed.

A number of substances affect glucose metabolism and may require dose adjustment of Xultophy.

The following substances may reduce the Xultophy requirement:
Anti-diabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the Xultophy requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormones and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the Xultophy requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of Xultophy.

Pharmacokinetic interactions

*In vitro* data suggest that the potential for pharmacokinetic drug interactions related to CYP interaction and protein binding is low for both liraglutide and insulin degludec.

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.

*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 Xultophy treatment in patients on warfarin or other coumarin derivatives more frequent monitoring of INR (International Normalised Ratio) is recommended.

*Paracetamol*
Liraglutide did not change the overall exposure 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. No dose adjustment for concomitant use of paracetamol is required.

*Atorvastatin*
Liraglutide did not change the overall exposure of atorvastatin to a clinical relevant degree following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. 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 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. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

*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. No dose adjustment of digoxin is required based on these results.

*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. No dose adjustment of lisinopril is required based on these results.

*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 delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with use of Xultophy, insulin degludec or liraglutide in pregnant women. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Xultophy should be discontinued.

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 toxicity, see section 5.3. The potential risk for humans is unknown.

Breast-feeding

There is no clinical experience with use of Xultophy during breast-feeding. It is not known whether insulin degludec or liraglutide is excreted in human milk. Because of lack of experience, Xultophy should not be used during breast-feeding.
In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma. Animal studies have shown that the transfer of liraglutide and metabolites of close structural relationship into milk was low. Non-clinical studies with liraglutide have shown a treatment-related reduction of neonatal growth in suckling rat pups (see section 5.3).

Fertility

There is no clinical experience with Xultophy in relation to fertility.
Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility. Apart from a slight decrease in the number of live implants, animal studies with liraglutide did not indicate harmful effects with respect to fertility.

## 4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. 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 hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

## 4.8 Undesirable effects

Summary of the safety profile

The Xultophy clinical development programme included approximately 1,900 patients treated with Xultophy.

The most frequently reported adverse reactions during treatment with Xultophy were hypoglycaemia and gastrointestinal adverse reactions (see section 'Description of selected adverse reactions' below).

Tabulated list of adverse reactions

Adverse reactions associated with Xultophy are given below, listed by system organ class and frequency. Frequency categories are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

**Table 1 Adverse reactions reported in phase 3 controlled studies**

| MedDRA System organ class | Frequency | Adverse Drug Reaction |
|---|---|---|
| Immune system disorders | Uncommon | Urticaria |
| | Uncommon | Hypersensitivity |
| | Unknown | Anaphylactic reaction |
| Metabolism and nutrition disorders | Very common | Hypoglycaemia |
| | Common | Decreased appetite |
| | Uncommon | Dehydration |
| Gastrointestinal disorders | Common | Nausea, diarrhoea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, gastroesophageal reflux disease, abdominal distension |
| | Uncommon | Eructation, flatulence |
| | Unknown | Pancreatitis (including necrotising pancreatitis ) |
| Hepatobiliary disorders | Uncommon | Cholelithiasis |
| | Uncommon | Cholecystitis |
| Skin and subcutaneous tissue disorders | Uncommon | Rash |
| | Uncommon | Pruritus |
| | Uncommon | Lipodystrophy acquired |
| General disorders and administration site condition | Common | Injection site reaction |
| | Unknown | Peripheral oedema |
| Investigation | Common | Increased lipase |
| | Common | Increased amylase |
| | Uncommon | Increased heart rate |

Description of selected adverse reactions

*Hypoglycaemia*

Hypoglycaemia may occur if the Xultophy dose is higher than required. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. For frequencies of hypoglycaemia, please see section 5.1.

*Allergic reactions*

Allergic reactions (manifested with signs and symptoms such as urticaria (0.3% of patients treated with Xultophy), rash (0.7%), pruritus (0.5%) and/or swelling of the face (0.2%)) have been reported for Xultophy. Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea, and oedema have been reported during marketed use of liraglutide. Anaphylactic reactions may potentially be life threatening.

*Gastrointestinal adverse reactions*

Gastrointestinal adverse reactions may occur more frequently at the beginning of Xultophy therapy and usually diminish within a few days or weeks on continued treatment. Nausea was reported in 7.8% of patients and was transient in nature for most patients. The proportion of patients reporting nausea per week at any point during treatment was below 4%. Diarrhoea and vomiting were reported in 7.5%

and 3.9% of patients, respectively. The frequency of nausea and diarrhoea was 'Common' for Xultophy and 'Very common' for liraglutide. In addition, constipation, dyspepsia, gastritis, abdominal pain, gastroesophageal reflux disease, abdominal distension, eructation, flatulence and decreased appetite have been reported in up to 3.6% of patients treated with Xultophy.

*Injection site reactions*
Injection site reactions (including injection site haematoma, pain, haemmorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) have been reported in 2.6% of patients treated with Xultophy. These reactions were usually mild and transitory and they normally disappear during continued treatment.

*Lipodystrophy*
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

*Increased heart rate*
Mean increase in heart rate from baseline of 2 to 3 beats per minute has been observed in clinical trials with Xultophy. The long-term clinical effects of the increase in heart rate have not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system ~~listed in Appendix V.~~

### 4.9 Overdose

Limited data are available with regard to overdose of Xultophy.

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

- Mild hypoglycaemic 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 hypoglycaemic 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting.
ATC code: A10AE56

Mechanism of action

Xultophy is a combination product consisting of insulin degludec and liraglutide having complementary mechanisms of action to improve glycaemic control.

Insulin degludec is a basal insulin that forms soluble multi-hexamers upon subcutaneous injection,

resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering effect of insulin degludec with a low day-to-day variability in insulin action.

Insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

The blood glucose-lowering effect of insulin degludec is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Liraglutide is a Glucagon-Like Peptide-1 (GLP-1) analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor (GLP-1R). Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption; binding to albumin; and higher enzymatic stability towards the dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors and improves glycaemic control by lowering fasting and postprandial blood glucose. Liraglutide stimulates insulin secretion and lowers inappropriately high glucagon secretion in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose-lowering also involves a minor delay in gastric emptying.

Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide, via specific activation of the GLP-1R, increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

Pharmacodynamic effects

Xultophy has a stable pharmacodynamic profile with a duration of action reflecting the combination of the individual action profiles of insulin degludec and liraglutide that allows for administration of Xultophy once daily at any time of the day with or without meals. Xultophy improves glycaemic control through the sustained lowering of fasting plasma glucose levels and postprandial glucose levels after all meals.

Postprandial glucose reduction was confirmed in a 4 hour standardised meal test sub-study in patients uncontrolled on metformin alone or in combination with pioglitazone. Xultophy decreased the postprandial plasma glucose excursion (mean over 4 hours) significantly more than insulin degludec. The results were similar for Xultophy and liraglutide.

Clinical efficacy and safety

*Add-on to oral glucose-lowering medicinal products*

*Add-on to metformin alone or in combination with pioglitazone*
The efficacy and safety of Xultophy compared to insulin degludec and liraglutide, all once daily, were studied in a 26-week randomised, controlled, open-label, treat-to-target trial in patients with type 2 diabetes mellitus with a 26 week extension. The starting dose of Xultophy and insulin degludec was 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide) and 10 units, respectively, and the dose was titrated twice weekly according to Table 2 below.
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 the maintenance dose of 1.8 mg was reached. The

maximum dose of Xultophy was 50 dose steps, while there was no maximum dose in the insulin degludec arm.

**Table 2 Titration of Xultophy and basal insulin**

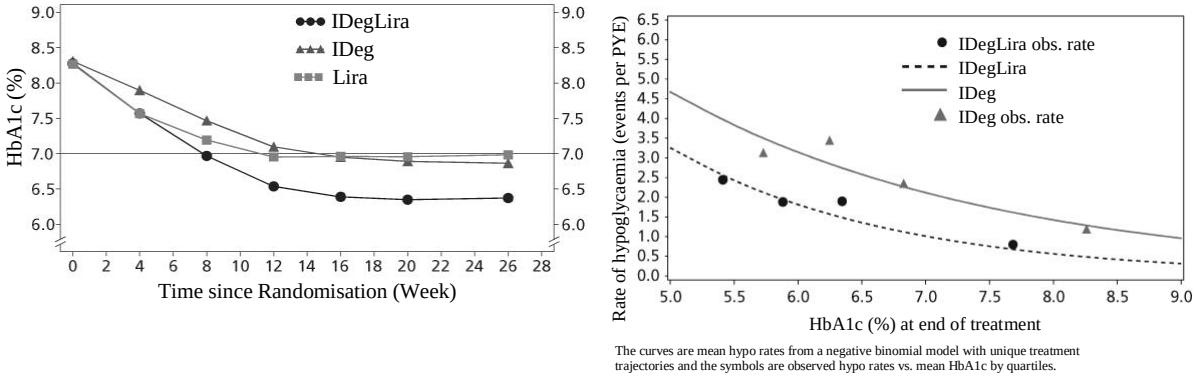
| **Pre-breakfast plasma glucose*** | | **Dose adjustment** | |
|---|---|---|---|
| mmol/L | mg/dL | Xultophy (dose steps) | Basal insulin (units) |
| < 4.0 | < 72 | -2 | -2 |
| 4.0-5.0 | 72-90 | 0 | 0 |
| > 5.0 | > 90 | +2 | +2 |

*Self-measured plasma glucose

The key results of the trial are listed in Figure 1 and Table 3.

60.4% of patients treated with Xultophy reached a target of $HbA_{1c}$ <7% without confirmed hypoglycaemic episodes after 26 weeks of treatment. The proportion was significantly larger than observed with insulin degludec (40.9%, odds ratio 2.28, p <0.0001) and similar to that observed with liraglutide (57.7%, odds ratio 1.13, p=0.3184).

Rates of confirmed hypoglycaemia were lower with Xultophy than with insulin degludec irrespective of the glycaemic control, see Figure 1.




IDegLira=Xultophy, IDeg=insulin degludec, Lira=liraglutide, obs. rate=observed rate, PYE=patient year of exposure

**Figure 1 Mean $HbA_{1c}$ (%) by treatment week (left) and rate of confirmed hypoglycaemia per patient year of exposure vs mean $HbA_{1c}$ (%) (right) in patients with type 2 diabetes mellitus inadequately controlled on metformin alone or in combination with pioglitazone**

The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia defined as an episode requiring assistance of another person was 0.01 (2 patients out of 825) for Xultophy, 0.01 (2 patients out of 412) for insulin degludec and 0.00 (0 patients out of 412) for liraglutide. The rate of nocturnal hypoglycaemic events was similar with Xultophy and insulin degludec treatment.

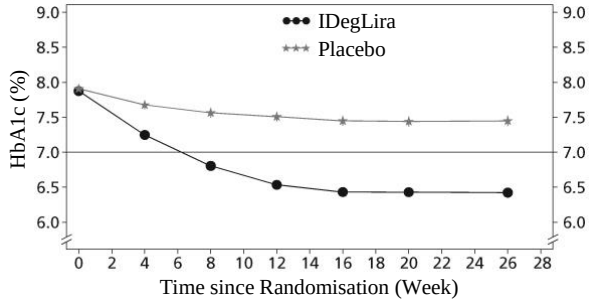
Patients treated with Xultophy overall experienced less gastrointestinal side effects than patients treated with liraglutide. This might be due to the slower increase in the dose of the liraglutide component during treatment initiation when using Xultophy as compared to using liraglutide alone.

*Long-term (52 week) data in patients inadequately controlled on metformin alone or in combination with pioglitazone*

The efficacy and safety of Xultophy were sustained up to 52 weeks of treatment. The reduction in $HbA_{1c}$ from baseline to 52 weeks was 1.84% with Xultophy with an estimated treatment difference of -0.65% compared to liraglutide (p<0.0001) and -0.46% compared to insulin degludec (p<0.0001). Body weight was reduced by 0.4 kg with an estimated treatment difference between Xultophy and insulin degludec of -2.80 kg (p<0.0001), and the rate of confirmed hypoglycaemia remained 1.8 events per patient year of exposure maintaining a significant reduction in overall risk of confirmed hypoglycaemia compared to insulin degludec.

*Add-on to sulfonylurea alone or in combination with metformin*
The efficacy and safety of Xultophy as add-on to sulfonylurea alone or in combination with metformin were studied in a 26-week randomised, placebo-controlled, double-blind, treat-to-target trial in 435 patients with type 2 diabetes mellitus of which 289 were treated with Xultophy. The starting dose of Xultophy was 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide), and the dose was titrated twice weekly. Titration was performed as outlined in Table 2 though with a titration target of 4-6 mmol/L.

The key results of the trial are listed in Figure 2 and Table 3.




IDegLira=Xultophy

**Figure 2 Mean $HbA_{1c}$ (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or in combination with metformin**

The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia was 0.02 (2 patients out of 288) for Xultophy and 0.00 (0 patients out of 146) for placebo.

**Table 3 Results from 26 week trials with Xultophy in patients with type 2 diabetes mellitus either inadequately controlled on metformin alone or in combination with pioglitazone (left) or inadequately controlled on sulfonylurea alone or in combination with metformin (right)**

| | **Previous treatment with metformin ± pioglitazone** | | | **Previous treatment with sulfonylurea ± metformin** | |
|---|---|---|---|---|---|
| | **Xultophy** | **Insulin degludec** | **Liraglutide** | **Xultophy** | **Placebo** |
| **N** | 833 | 413 | 414 | 289 | 146 |
| **$HbA_{1c}$ (%)** | | | | | |
| Baseline→End of trial | 8.3→6.4 | 8.3→6.9 | 8.3→7.0 | 7.9→6.4 | 7.9→7.4 |
| Mean change | -1.91 | -1.44 | -1.28 | -1.45 | -0.46 |
| *Estimated difference* | | *-0.47[AB] [-0.58; -0.36]* | *-0.64[AB] [-0.75; -0.53]* | | *-1.02[AB] [-1.18; -0.87]* |
| **Patients (%) achieving $HbA_{1c}$ <7%** | | | | | |
| All patients | 80.6 | 65.1 | 60.4 | 79.2 | 28.8 |
| *Estimated odds ratio* | | *2.38[B] [1.78; 3.18]* | *3.26[B] [2.45; 4.33]* | | *11.95[B] [7.22; 19.77]* |
| **Patients (%) achieving $HbA_{1c}$ ≤6.5%** | | | | | |
| All patients | 69.7 | 47.5 | 41.1 | 64.0 | 12.3 |
| *Estimated odds ratio* | | *2.82[B] [2.17; 3.67]* | *3.98[B] [3.05; 5.18]* | | *16.36[B] [9.05; 29.56]* |
| **Rate of confirmed hypoglycaemia* per patient year of exposure (percentage of patients)** | 1.80 (31.9%) | 2.57 (38.6%) | 0.22 (6.8%) | 3.52 (41.7%) | 1.35 (17.1%) |
| *Estimated ratio* | | *0.68[AC] [0.53; 0.87]* | *7.61[B] [5.17; 11.21]* | | *3.74[B] [2.28; 6.13]* |
| **Body Weight (kg)** | | | | | |
| Baseline→End of trial | 87.2→86.7 | 87.4→89.0 | 87.4→84.4 | 87.2→87.7 | 89.3→88.3 |
| Mean change | -0.5 | 1.6 | -3.0 | 0.5 | -1.0 |
| *Estimated difference* | | *-2.22[AB] [-2.64; -1.80]* | *2.44[B] [2.02; 2.86]* | | *1.48[B] [0.90; 2.06]* |
| **FPG (mmol/L)** | | | | | |
| Baseline→End of trial | 9.2→5.6 | 9.4→5.8 | 9.0→7.3 | 9.1→6.5 | 9.1→8.8 |
| Mean change | -3.62 | -3.61 | -1.75 | -2.60 | -0.31 |

| | | | | | |
|---|---|---|---|---|---|
| *Estimated difference* | | *-0.17 [-0.41; 0.07]* | *-1.76[B] [-2.0; -1.53]* | | *-2.30[B] [-2.72; -1.89]* |
| **Dose End of trial** | | | | | |
| Insulin degludec (units) | 38 | 53 | - | 28 | - |
| Liraglutide (mg) | 1.4 | - | 1.8 | 1.0 | - |
| *Estimated difference, insulin degludec dose* | | *-14.90[AB] [-17.14; -12.66]* | | | - |

Baseline, End of trial and change values are observed Last observation carried forward. The 95% confidence interval is stated in '[]'
*Confirmed hypoglycaemia defined as severe hypoglycaemia (episode requiring assistance of another person) and/or minor hypoglycaemia (plasma glucose <3.1 mmol/L irrespective of symptoms)
[A] Endpoints with confirmed superiority of Xultophy vs comparator
[B] p<0.0001
[C] p<0.05

*Transfer from GLP-1 receptor agonist therapy*

The efficacy and safety of Xultophy (once-daily) compared to unchanged GLP-1 receptor agonist therapy (dosed according to label), were studied in a 26-weeks randomised, open-label, treat-to-target trial in patients with type 2 diabetes mellitus inadequately controlled on a GLP-1 receptor agonist and metformin alone (74.2%) or in combination with pioglitazone (2.5%), sulfonylurea (21.2%) or both (2.1%).

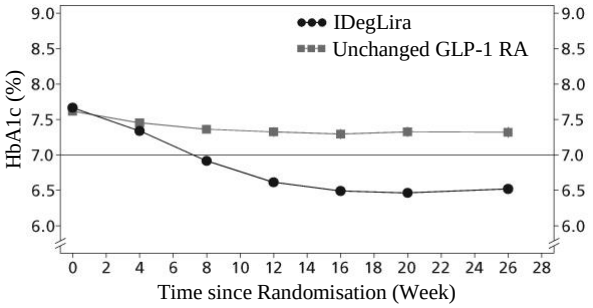
The starting dose of Xultophy was 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) and the dose was titrated twice weekly according to Table 2. Patients in the GLP-1 receptor agonist arm were to continue pre-trial GLP-1 receptor agonist treatment.

The key results of the trial are listed in Table 4 and Figure 3.

**Table 4 Results of a 26 week trial with Xultophy in patients with type 2 diabetes mellitus inadequately controlled on GLP-1 receptor agonists**

| | **Previous treatment with GLP-1 receptor agonist** | |
|---|---|---|
| | **Xultophy** | **GLP-1 receptor agonist** |
| **N** | 292 | 146 |
| **$HbA_{1c}$ (%)** | | |
| Baseline→End of trial | 7.8→6.4 | 7.7→7.4 |
| Mean change | -1.3 | -0.3 |
| *Estimated difference* | | *-0.94[AB] [-1.11; -0.78]* |
| **Patients (%) achieving $HbA_{1c}$ <7%** | | |
| All patients | 75.3 | 35.6 |
| *Estimated odds ratio* | | *6.84[B] [4.28; 10.94]* |
| **Patients (%) achieving $HbA_{1c}$ ≤6.5%** | | |
| All patients | 63.0 | 22.6 |
| *Estimated odds ratio* | | *7.53[B] [4.58; 12.38]* |
| **Rate of confirmed hypoglycaemia* per patient year of exposure (percentage of patients)** | 2.82 (32.0%) | 0.12 (2.8%) |
| *Estimated ratio* | | *25.36[B] [10.63; 60.51]* |
| **Body Weight (kg)** | | |
| Baseline→End of trial | 95.6→97.5 | 95.5→94.7 |
| Mean change | 2.0 | -0.8 |
| *Estimated difference* | | *2.89[B] [2.17; 3.62]* |
| **FPG (mmol/L)** | | |
| Baseline→End of trial | 9.0→6.0 | 9.4→8.8 |
| Mean change | -2.98 | -0.60 |
| *Estimated difference* | | *-2.64[B] [-3.03; -2.25]* |
| **Dose End of trial** | | |
| Insulin degludec (units) | 43 | *GLP-1 receptor agonist dose was to be continued unchanged from baseline* |
| Liraglutide (mg) | 1.6 | |
| *Estimated difference, insulin degludec dose* | | |

Baseline, End of trial and change values are observed Last observation carried forward. The 95% confidence interval is stated in '[]'
*Confirmed hypoglycaemia defined as severe hypoglycaemia (episode requiring assistance of another person) and/or minor hypoglycaemia (plasma glucose<3.1 mmol/L irrespective of symptoms)
[A] Endpoints with confirmed superiority of Xultophy vs comparator
[B] p<0.001




IDegLira=Xultophy, GLP-1 RA=GLP-1 receptor agonist

**Figure 3 Mean $HbA_{1c}$ (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on GLP-1 receptor agonists**

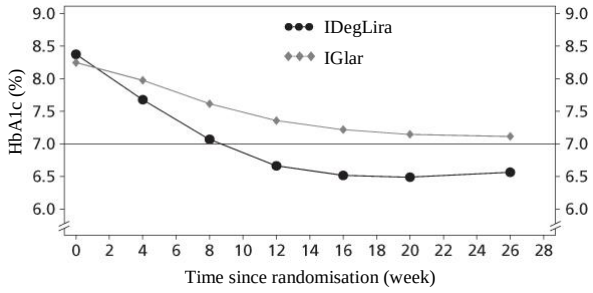
The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia was 0.01 (1 patient out of 291) for Xultophy and 0.00 (0 patients out of 199) for GLP-1 receptor agonists.

*Transfer from basal insulin therapies*

The efficacy and safety of Xultophy compared to insulin glargine, both once daily, 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 starting dose of Xultophy was 16 dose steps and the starting dose of insulin glargine was equal to the pre-trial daily dose. The dose in both arms was titrated twice weekly according to Table 2. The maximum allowed dose was 50 dose steps for Xultophy while there was no maximum dose for insulin glargine.

The key results of the trial are listed in Table 5 and Figure 4.

54.3% of patients treated with Xultophy reached the $HbA_{1c}$ target of <7% without confirmed hypoglycaemic episodes compared to 29.4% of patients treated with insulin glargine (odds ratio 3.24, p<0.001).




IDegLira=Xultophy, IGlar=insulin glargine

**Figure 4 Mean $HbA_{1c}$ (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine**

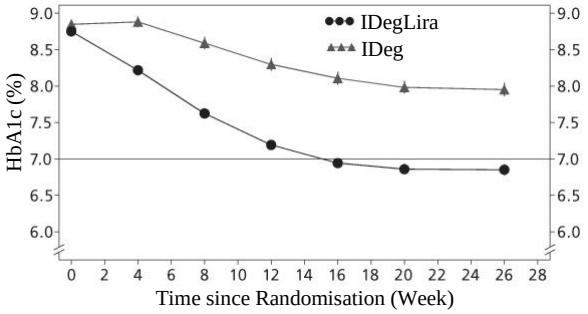
The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia was 0.00 (0 patients out of 278) for Xultophy and 0.01 (1 patient out of 279) for insulin glargine. The rate of nocturnal hypoglycaemic events was significantly lower with Xultophy compared to insulin glargine (estimated treatment ratio 0.17, p<0.001).

The efficacy and safety of Xultophy compared to insulin degludec, both once daily, 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 sulfonylurea/glinides. Basal insulin and sulfonylurea/glinides were discontinued at randomisation. The starting dose of Xultophy and insulin degludec was 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) and 16 units, respectively, and the dose was titrated twice weekly according to Table 2. The maximum allowed dose was 50 dose steps for Xultophy and 50 units for insulin

degludec.

The key results of the trial are listed in Table 5 and Figure 5.

48.7% of patients reached the $HbA_{1c}$ target of <7% without confirmed hypoglycaemic episodes, which was a significantly higher proportion than observed with insulin degludec (15.6%, odds ratio 5.57, p<0.0001).




IDegLira=Xultophy, IDeg=insulin degludec

**Figure 5 Mean $HbA_{1c}$ (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on basal insulin**

The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia was 0.01 (1 patient out of 199) for Xultophy and 0.00 (0 patients out of 199) for insulin degludec. The rate of nocturnal hypoglycaemic events was similar with Xultophy and insulin degludec treatment.

**Table 5 Results from two 26 week trials with Xultophy in patients with type 2 diabetes mellitus either inadequately controlled on insulin glargine (left) or basal insulin (right)**

| | **Previous treatment with insulin glargine** | | | **Previous treatment with basal insulin (NPH, insulin detemir, insulin glargine)** | |
|---|---|---|---|---|---|
| | **Xultophy** | **Insulin glargine, no limitation to dose** | | **Xultophy** | **Insulin degludec, maximum 50 units allowed** |
| **N** | 278 | 279 | | 199 | 199 |
| **$HbA_{1c}$ (%)** | | | | | |
| Baseline→End of trial | 8.4→6.6 | 8.2→7.1 | | 8.7→6.9 | 8.8→8.0 |
| Mean change | -1.81 | -1.13 | | -1.90 | -0.89 |
| *Estimated difference* | | *-0.59[AB] [-0.74; -0.45]* | | | *-1.05[AB] [-1.25; -0.84]* |
| **Patients (%) achieving $HbA_{1c}$ <7%** | | | | | |
| All patients | 71.6 | 47.0 | | 60.3 | 23.1 |
| *Estimated odds ratio* | | *3.45[B] [2.36;5.05]* | | | *5.44[B] [3.42; 8.66]* |
| **Patients (%) achieving $HbA_{1c}$ ≤6.5%** | | | | | |
| All patients | 55.4 | 30.8 | | 45.2 | 13.1 |
| *Estimated odds ratio* | | *3.29[B] [2.27; 4.75]* | | | *5.66[B] [3.37; 9.51]* |
| **Rate of confirmed hypoglycaemia* per patient year of exposure (percentage of patients)** | 2.23 (28.4%) | 5.05 (49.1%) | | 1.53 (24.1%) | 2.63 (24.6%) |
| *Estimated ratio* | | *0.43[AB] [0.30;0.61]* | | | *0.66 [0.39; 1.13]* |
| **Body Weight (kg)** | | | | | |
| Baseline→End of trial | 88.3→86.9 | 87.3→89.1 | | 95.4→92.7 | 93.5→93.5 |
| Mean change | -1.4 | 1.8 | | -2.7 | 0.0 |
| *Estimated difference* | | *-3.20[AB] [-3.77; -2.64]* | | | *-2.51[B] [-3.21; -1.82]* |
| **FPG (mmol/L)** | | | | | |
| Baseline→End of trial | 8.9→6.1 | 8.9→6.1 | | 9.7→6.2 | 9.6→7.0 |
| Mean change | -2.83 | -2.77 | | -3.46 | -2.58 |
| *Estimated difference* | | *-0.01 [-0.35;0.33]* | | | *-0.73[C] [-1.19; -0.27]* |
| **Dose End of trial** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Insulin (units) | 41 | 66[D] | | 45 | 45 |
| Liraglutide (mg) | 1.5 | - | | 1.7 | - |
| *Estimated difference, basal insulin dose* | | *-25.47[B] [-28.90;-22.05]* | | | *-0.02 [-1.88; 1.84]* |

Baseline, End of trial and change values are observed Last observation carried forward. The 95% confidence interval is stated in '[]'
*Confirmed hypoglycaemia defined as severe hypoglycaemia (episode requiring assistance of another person) and/or minor hypoglycaemia (plasma glucose<3.1 mmol/L irrespective of symptoms)
[A] Endpoints with confirmed superiority of Xultophy vs comparator
[B] p<0.0001
[C] p<0.05
[D] The average pre-trial dose of insulin glargine was 32 units

*Other clinical data*

*Insulin secretion/beta-cell function*
Xultophy improves beta-cell function compared to insulin degludec as measured by the homeostasis model assessment for beta-cell function (HOMA-β). Improved insulin secretion compared to insulin degludec in response to a standardised meal test was demonstrated in 260 patients with type 2 diabetes after 52 weeks treatment. No data is available beyond 52 weeks of treatment.

*Blood pressure*
In patients inadequately controlled on metformin alone or in combination with pioglitazone, Xultophy reduced mean systolic blood pressure by 1.8 mmHg compared to a reduction of 0.7 mmHg with insulin degludec and 2.7 mmHg with liraglutide. In patients inadequately controlled on sulfonylurea alone or in combination with metformin, the reduction was 3.5 mmHg with Xultophy and 3.2 mmHg with placebo. The differences were not statistically significant. In two trials with patients inadequately controlled on basal insulin, systolic blood pressure was reduced by 5.4 mmHg with Xultophy and 1.7 mmHg with insulin degludec, with a statistically significant estimated treatment difference of -3.71 mmHg (p=0.0028), and reduced by 3.7 mmHg with Xultophy vs 0.2 mmHg with insulin glargine, with a statistically significant estimated treatment difference of -3.57 mmHg (p<0.001).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Xultophy in all subsets of the paediatric population for treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Overall, the pharmacokinetics of insulin degludec and liraglutide were not affected in a clinically relevant manner when administered as Xultophy compared with independent injections of insulin degludec and liraglutide.

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

Absorption

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 equivalent following administration of Xultophy versus liraglutide alone while $C_{max}$ was lower by 23%. The differences are considered of no clinical relevance since Xultophy is initiated and titrated according to the individual patient's blood glucose targets.

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).

Biotransformation

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

*Liraglutide*
During 24 hours 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 metabolised in a similar manner to large proteins without a specific organ having been identified as major route of elimination.

Elimination

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

Special populations

*Elderly patients*
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.

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

*Ethnic origin*
Ethnic origin had no clinically relevant effect on the pharmacokinetics of Xultophy based on results from a population pharmacokinetic analysis including White, Black, Indian, Asian and Hispanic groups.

*Renal impairment*
*Insulin degludec*
There is no difference in the pharmacokinetics of insulin degludec between healthy subjects and patients with renal impairment.

*Liraglutide*
Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, in patients with mild (creatinine clearance, CrCl 50–80 mL/min), moderate (CrCl 30–50 mL/min), and severe (CrCl <30 mL/min) renal impairment and in end-stage renal disease requiring dialysis, respectively. Similarly, in a 26-week clinical trial, patients with type 2 diabetes and moderate renal impairment (CrCL 30–59 mL/min) had 26% lower liraglutide exposure when compared with a separate trial including patients with type 2 diabetes with normal renal function or mild renal impairment.

*Hepatic impairment*
*Insulin degludec*
There is no difference in the pharmacokinetics of insulin degludec between healthy subjects and patients with hepatic impairment.

*Liraglutide*

The pharmacokinetics of liraglutide was evaluated in patients with varying degrees of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 13–23% in patients with mild to moderate hepatic impairment compared to healthy subjects. Exposure was significantly lower (44%) in patients with severe hepatic impairment (Child Pugh score >9).

*Paediatric population*
No studies have been performed with Xultophy in children and adolescents below 18 years of age.

### 5.3 Preclinical safety data

The non-clinical development programme for insulin degludec/liraglutide included pivotal combination toxicity studies of up to 90 days duration in a single relevant species (Wistar rats) to support the clinical development programme. Local tolerance was assessed in rabbits and pigs.

Non-clinical safety data revealed no safety concern for humans based on repeated dose toxicity studies.

The local tissue reactions in the two studies in rabbits and pigs, respectively, were limited to mild inflammatory reactions.

No studies have been conducted with the insulin degludec/liraglutide combination to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based upon studies with insulin degludec and liraglutide individually.

*Insulin degludec*
Non-clinical data reveal no safety concern for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction.
The ratio of mitogenic relative to metabolic potency for insulin degludec is unchanged compared to human insulin.

*Liraglutide*
Non-clinical data reveal no special hazards for human based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity. Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. No other treatment-related tumours have been found.

Animal studies did not indicate direct harmful effects with respect to fertility but slightly increased early embryonic deaths at the highest dose. Dosing with liraglutide during mid-gestation caused a reduction in maternal weight and foetal growth with equivocal effects on ribs in rats and skeletal variation in the rabbit. Neonatal growth was reduced in rats while exposed to liraglutide, and persisted in the post-weaning period in the high dose group. It is unknown whether the reduced pup growth is caused by reduced pup milk intake due to a direct GLP-1 effect or reduced maternal milk production due to decreased caloric intake.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Glycerol
Phenol
Zinc acetate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

Water for injections

### 6.2 Incompatibilities

Substances added to Xultophy may cause degradation of the active substances.

Xultophy must not be added to infusion fluids.

This medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

2 years.

After first opening, the product can be stored for 21 days at a maximum temperature of 30°C. The product should be discarded 21 days after first opening.

### 6.4 Special precautions for storage

Before first opening: Store in a refrigerator (2°C – 8°C). Keep away from the freezing element. Do not freeze. Keep the cap on the pre-filled pen in order to protect from light.

After first opening: Store at a maximum of 30°C or store in a refrigerator (2°C – 8°C). Do not freeze. Keep the cap on the pre-filled pen in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

3 mL solution in a cartridge (type 1 glass) with a plunger (halobutyl) and a stopper (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polycarbonate and acrylonitrile butadiene styrene.

Pack sizes of 1, 3, 5 and multipack containing 10 (2 packs of 5) pre-filled pens.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

The pre-filled pen is for use by one person only.

Xultophy must not be used if the solution does not appear clear and colourless.

Xultophy which has been frozen must not be used.

The patient should discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For detailed instructions for use, see the package leaflet.

## 7. MARKETING AUTHORISATION HOLDER

~~Novo Nordisk A/S~~
~~Novo Allé~~
~~DK-2880 Bagsværd~~
~~Denmark~~
Novo Nordisk Pharma (Thailand) Ltd., Bangkok, Thailand

## 8. MARKETING AUTHORISATION NUMBERS

~~EU/1/14/947/001~~
~~EU/1/14/947/002~~
~~EU/1/14/947/003~~
~~EU/1/14/947/004~~
Thai Reg.No.

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: ~~18 September 2014~~ Approval date from Thai FDA

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the ~~European Medicines Agency http://www.ema.europa.eu.~~ Thai FDA