Regulatory Operations

Insert: 2010-508x616-008
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Colour:
PMS 280C +
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Xultophy®

100 units/ml + 3.6 mg/ml
Solution for injection.

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 *List of excipients.*

Pharmaceutical form

Solution for injection.
Clear, colourless, isotonic solution.

Clinical particulars

Therapeutic indications

Xultophy® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control, and the populations studied, see *Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction* and *Pharmacodynamic properties.*

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 antidiabetic treatment. When Xultophy® is added to sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered (see *Special warnings and precautions for use*).

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 *Pharmacodynamic properties*). 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 any insulin regimen that includes a basal insulin component
Therapy with other insulin regimens should be discontinued prior to initiation of Xultophy®. When transferring from any other insulin therapy that includes a basal insulin component, the recommended starting dose of Xultophy® is 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) (see *Special warnings and precautions for use* and *Pharmacodynamic properties*). The recommended starting dose should not be exceeded, but may be reduced to avoid hypoglycaemia in selected cases. 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.

Renal impairment
When Xultophy® is used in patients with mild, moderate or severe 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 end-stage renal disease (see *Pharmacodynamic properties* and *Pharmacokinetic properties*).

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 *Pharmacokinetic properties*).

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 should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see *Special warnings and precautions for use and Undesirable effects*). For further instructions on administration, see *Special precautions for disposal and other handling.*

Xultophy® must not be drawn from the cartridge of the pre-filled pen into a syringe (see *Special warnings and precautions for use*).

Patients should be instructed to always use a new needle. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see *Special precautions for disposal and other handling*).

Contraindications

Hypersensitivity to either or both active substances or to any of the excipients listed in *List of excipients.*

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 *Undesirable effects*) 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 antidiabetic treatment may lead to hyperglycaemia and potentially to hyperosmolar coma. In case of discontinuation of Xultophy®, ensure that instruction for initiation of alternative antidiabetic medication is followed. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased requirement for antidiabetic 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.

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 glycaemic 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 hypoglycaemia. 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.

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
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists, including liraglutide. 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.

Thyroid adverse events
Thyroid adverse events, such as goitre have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, and in particular in patients with pre-existing thyroid disease. 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.

Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

To avoid dosing errors and potential overdose, patients and healthcare professionals should never use a syringe to draw the medicinal product from the cartridge in the pre-filled pen.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see *Special precautions for disposal and other handling*).

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

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and Xultophy® is therefore not recommended for use in these patients.

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

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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:
Antidiabetic 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.

Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with the 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 *Preclinical safety data.* The potential risk for humans is unknown.

Breast-feeding

There is no clinical experience with the 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 *Preclinical safety data*).

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.

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.

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 *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
	Not known	Cutaneous amyloidosis†
General disorders and administration site condition	Common	Injection site reaction
	Unknown	Peripheral oedema
Investigation	Common	Increased lipase
	Common	Increased amylase
	Uncommon	Increased heart rate

† ADR from postmarketing sources.

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 *Pharmacodynamic properties.*

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.

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see *Special warnings and precautions for use*).

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®. In the LEADER trial, no long-term clinical impact of increased heart rate on the risk of cardiovascular events was observed with liraglutide (a component of Xultophy®) (see *Pharmacodynamic properties*).

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.

Pharmacological properties

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.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

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 substudy 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

The safety and efficacy of Xultophy® were evaluated in seven randomised, controlled, parallel group phase 3 trials in different populations of subjects with type 2 diabetes defined by previous antidiabetes treatment. Comparator treatments comprised basal insulin, GLP-1 RA therapy, placebo and a basal bolus regimen. The trials were of 26 weeks duration randomising between 199 and 833 patients to Xultophy®. One study was further extended to 52 weeks. In all trials, the starting dose was given according to label and a twice-weekly titration regimen for Xultophy® was used (see Table 2). The same titration algorithm was applied for basal insulin comparators. In six studies, Xultophy® produced clinically and statistically significant improvements in glycaemic control versus comparators as measured by glycated haemaglobin A_{1c} (HbA_{1c}), whereas one study demonstrated a similar reduction of HbA_{1c} in both treatment arms.

Table 2 Titration of Xultophy®

Pre-breakfast plasma glucose*		Dose adjustment (twice weekly)
mmol/l	mg/dl	Xultophy® (dose steps)
<4.0	<72	-2
4.0–5.0	72–90	0
>5.0	>90	+2

*Self-measured plasma glucose. In the trial investigating Xultophy® as add on to sulfonylurea the target was 4.0-6.0 mmol/l

Glycaemic control

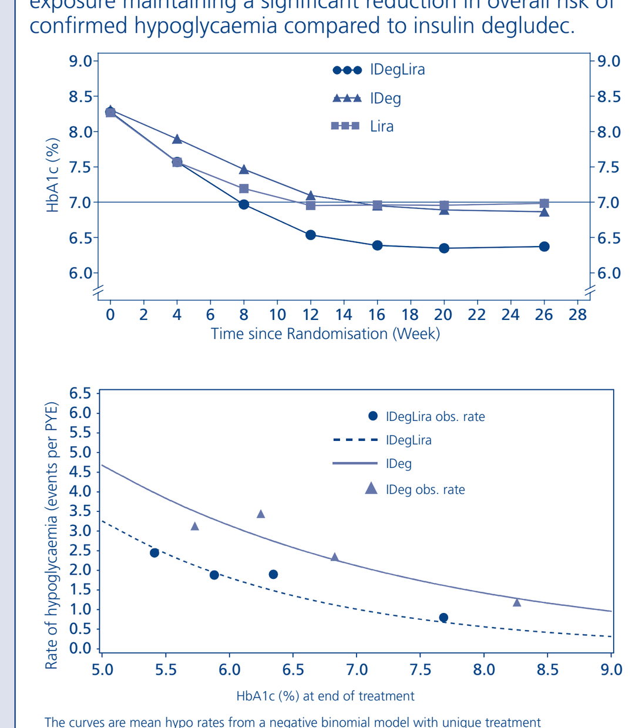
Add-on to oral glucose-lowering medicinal products
Adding Xultophy® to metformin alone or in combination with pioglitazone in a 26-week randomised, controlled, open-label trial resulted in 60.4% of patients treated with Xultophy® reaching a target of HbA_{1c} <7% without confirmed hypoglycaemic episodes 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).

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

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

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.

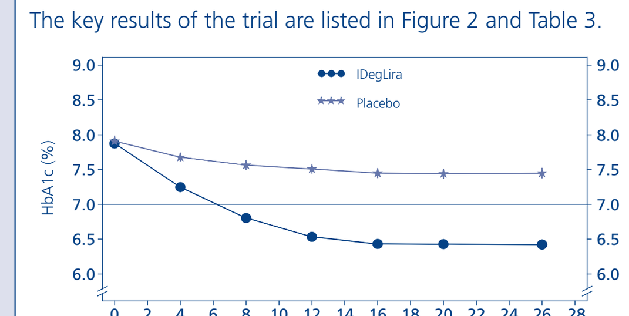


IDegLira=Xultophy®, IDeg=insulin degludec, Lira=liraglutide, obs. rate=observed rate, PYE=patient year of exposure

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

Xultophy® as add-on to sulfonylurea alone or in combination with metformin were studied in a 26-week randomised, placebo-controlled, double-blind trial.

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 at 26-weeks – Add on to oral glucose-lowering medicinal products

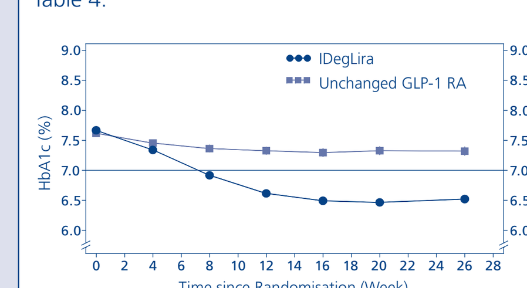
	Add on to metformin ± pioglitazone			Add on to sulfonylurea ± metformin	
	Xultophy®	**Insulin degludec**	**Liraglutide**	**Xultophy®**	**Placebo**
N	833	413	414	289	146
HbA_{1c} (%)					
Baseline→End of trial	8.3→6.4	8.3→6.9	8.3→7.0	7.9→6.4	7.9→7.4
Mean change	-1.91	-1.44	-1.28	-1.45	-0.46
Estimated 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.

In an open label trial comparing the efficacy and safety of Xultophy® and insulin glargine 100 units/ml, both as add-on to SGLT2i ± OAD, Xultophy® was superior to insulin glargine in reducing mean HbA_{1c} after 26 weeks by 1.9% (from 8.2% to 6.3%) versus 1.7% (from 8.4% to 6.7%) with an estimated treatment difference of -0.36% [-0.50; -0.21]. Compared to baseline, Xultophy® resulted in an unchanged mean body weight compared to a mean weight increase of 2.0 kg for patients treated with insulin glargine (estimated treatment difference -1.92 kg [95% CI: -2.64; -1.19]). The percentage of patients experiencing severe or blood-glucose confirmed symptomatic hypoglycaemia was 12.9% in the Xultophy® group and 19.5% in the insulin glargine group (estimated treatment ratio 0.42 [95% CI: 0.23; 0.75]). The mean daily insulin dose at end of trial was 36 units for patients treated with Xultophy® and 54 units for patients treated with insulin glargine.

Transfer from GLP-1 receptor agonist therapy
Transfer from GLP-1 receptor agonist to Xultophy® compared to unchanged GLP-1 receptor agonist therapy (dosed according to label) were studied in a 26-weeks randomised, open-label 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 key results of the trial are listed in Figure 3 and Table 4.



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.

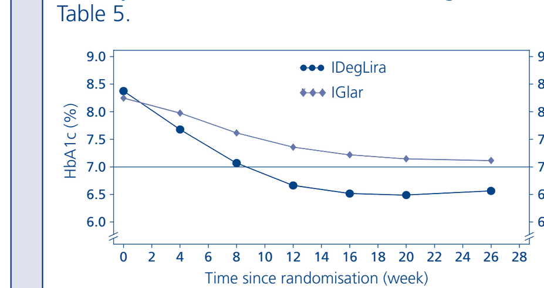
Table 4 Results at 26-weeks – Transfer from GLP-1 receptor agonists

	Transfer from 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.

Transfer from basal insulin therapies
Transfer of patients from insulin glargine (100 units/ml) to Xultophy® or intensification of insulin glargine in patients inadequately controlled on insulin glargine (20–50 units) and metformin were studied in a 26 week trial. The maximum allowed dose in the trial was 50 dose steps for Xultophy® whereas there was no maximum dose for insulin glargine. 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).

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



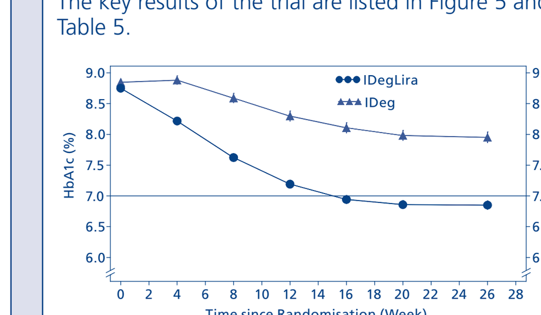
IDegLira=Xultophy®, IGlar=insulin glargine

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).

In a second trial, the transfer from basal insulin to Xultophy® or insulin degludec was investigated in a 26-week randomised, double-blind trial in patients 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 maximum allowed dose was 50 dose steps for Xultophy® and 50 units for insulin degludec. 48.7% of patients treated with Xultophy® reached the HbA_{1c} target of <7% without confirmed hypoglycaemic episodes. This was a significantly higher proportion than observed with insulin degludec (15.6%, odds ratio 5.57, p<0.0001).

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



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

8-9553-00-018-1

Xultophy®
100 units/ml + 3.6 mg/ml solution for injection
insulin degludec + liraglutide

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

novo nordisk®

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 at 26-weeks – Transfer from basal insulin

	Transfer from insulin glargine (100 units/ml)		Transfer from 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[a][B]* *[-0.74; -0.45]*		*-1.05[a][B]* *[-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[a][B]* *[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[a][B]* *[-3.77; -2.64]*		*-2.51[a]* *[-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[b]	45	45
Liraglutide (mg)	1.5	-	1.7	-
Estimated difference, basal insulin dose		*-25.47[a]* *[-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; [b] The average pre-trial dose of insulin glargine was 32 units.

Treatment with Xultophy® compared to a basal-bolus insulin regimen consisting of basal insulin (insulin glargine 100 units/ml) in combination with bolus insulin (insulin aspart) studied in a 26-week trial in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine and metformin demonstrated a similar reduction of HbA_{1c} in the two groups (mean value from 8.2% to 6.7% in both groups). In both groups 66%–67% achieved HbA_{1c} <7%. Compared to baseline, there was a mean reduction in body weight of 0.9 kg for Xultophy® and a mean increase of 2.6 kg for patients treated with a basal-bolus regimen and the estimated treatment difference was -3.57 kg [95% CI: -4.19; -2.95]. The percentage of patients experiencing severe or blood-glucose confirmed symptomatic hypoglycaemia was 19.8% in the Xultophy® group and 52.6% in the basal-bolus insulin group, and the estimated rate ratio was 0.11 [95% CI: 0.08–0.17]. The total daily insulin dose at end of trial was 40 units for patients treated with Xultophy® and 84 units (52 units of basal insulin and 32 units of bolus insulin) for patients treated with a basal-bolus insulin regimen.

Cardiovascular Safety
No cardiovascular outcomes trials have been performed with Xultophy®.

Liraglutide (Victoza®)
The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial, was a multicentre, placebo-controlled, double-blind clinical trial. 9,340 patients were randomly allocated to either liraglutide (4,668) or placebo (4,672), both in addition to standards of care for HbA_{1c} and cardiovascular (CV) risk factors. Primary outcome or vital status at end of trial was available for 99.7% and 99.6% of participants randomised to liraglutide and placebo, respectively. The duration of observation was minimum 3.5 years and up to a maximum of 5 years. The study population included patients ≥65 years (n=4,329) and ≥75 years (n=836) and patients with mild (n=3,907), moderate (n=1,934) or severe (n=224) renal impairment. The mean age was 64 years and the mean BMI was 32.5 kg/m². The mean duration of diabetes was 12.8 years.

The primary endpoint was the time from randomisation to first occurrence of any major adverse cardiovascular events (MACE): CV death, non-fatal myocardial infarction or non-fatal stroke. Liraglutide was superior in preventing MACE vs placebo (Figure 6).

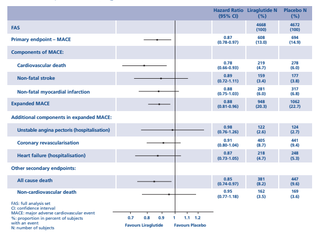
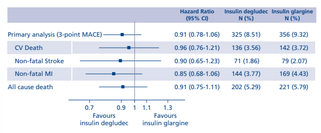


Figure 6 Forest plot of analyses of individual cardiovascular event types – FAS population

A reduction in HbA_{1c} from baseline to month 36 was observed with liraglutide vs placebo, in addition to standard of care (-1.16% vs -0.77%; estimated treatment difference [ETD] -0.40% [-0.45; -0.34]).

Insulin degludec (Tresiba®)
DEVOTE was a randomised, double-blind, and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of insulin degludec versus insulin glargine (100 units/ml) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events.
The primary analysis was time from randomisation to first occurrence of a 3-component major adverse cardiovascular event (MACE) defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The trial was designed as a non-inferiority trial to exclude a pre-specified risk margin of 1.3 for the hazard ratio (HR) of MACE comparing insulin degludec to insulin glargine. The cardiovascular safety of insulin degludec as compared to insulin glargine was confirmed (HR 0.91 [0.78; 1.06]) (Figure 7).

At baseline, HbA_{1c} was 8.4% in both treatment groups and after 2 years HbA_{1c} was 7.5% both with insulin degludec and insulin glargine.



N: Number of subjects with a first EAC confirmed event during trial. %: Percentage of subjects with a first EAC confirmed event relative to the number of randomised subjects. EAC: Event adjudication committee. CV: Cardiovascular. MI: Myocardial infarction. CI: 95% confidence interval.

Figure 7 Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE

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 of 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 three 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), 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) and reduced by 4.5 mmHg with Xultophy® vs 1.16 mmHg with insulin glargine U100 plus insulin aspart, with a statistically significant estimated treatment difference of -3.70 mmHg (p=0.0003).

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 [³H]-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.

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.

Pharmaceutical Particulars
List of excipients
Glycerol, phenol, zinc acetate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

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.

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: The product can be stored for 21 days at a maximum of 30°C or stored in a refrigerator (2°C – 8°C). The product should be discarded 21 days after first opening. Do not freeze. Keep the cap on the pre-filled pen in order to protect from light.

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.

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.
A new needle must always be attached before each use.
Needles must not be re-used. The patient should discard the needle after each injection.
In the event of blocked needles, patients must follow the instructions described in the instructions for use.

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

See detailed instruction for use accompanying this leaflet.

Produced by
Novo Nordisk A/S
Novo Allé, DK-2880 Bagsværd, Denmark

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 'dose steps'. One dose step contains 1 unit insulin degludec + 0.036 mg liraglutide.

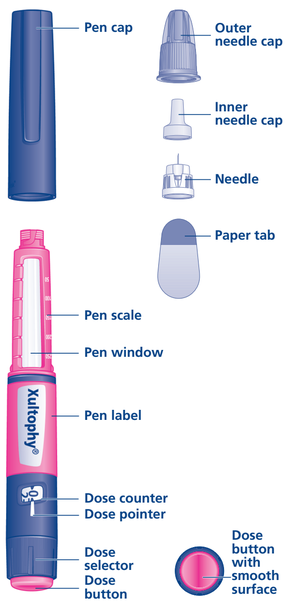
Your pen is a pre-filled dial-a-dose pen. It contains 3 ml of Xultophy® solution. It delivers doses from:
– 1 dose step
– to a **maximum of 50 dose steps** (50 units insulin degludec + 1.8 mg liraglutide)

Your pen delivers doses in increments of 1 dose step. Do not do any conversion of your dose. The dose steps dialled equal the number shown in the dose counter.

Your pen is designed 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.

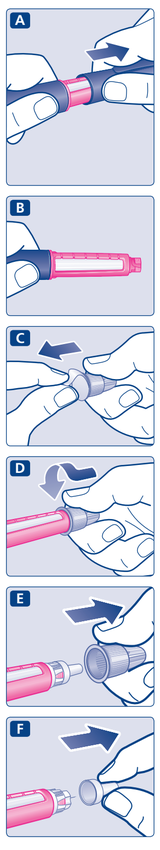
Important information
Pay special attention to these notes as they are important for safe use of the pen.

Xultophy® pre-filled pen and needle (example)



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.

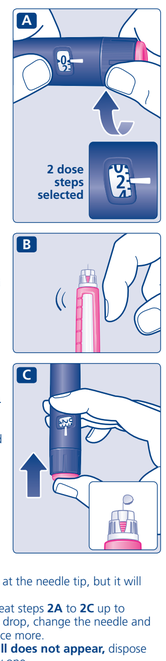


A drop of solution may appear at the needle tip. This is normal, but you must still check the flow.
Do not attach a new needle to your pen until you are ready to take your injection.

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 dose steps.** Make sure the dose counter shows 2.
- The dose counter and the dose pointer show how many dose steps 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.



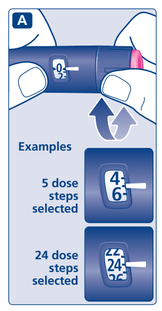
A small drop may remain at the needle tip, but it will not be injected.
If no drop appears, repeat steps **2A** to **2C** up to 6 times. If there is still no drop, change the needle and repeat steps **2A** to **2C** once more.
If a drop of solution still does not appear, dispose of the pen and use a 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 dose steps.
If you select a wrong dose, you can turn the dose selector forward or backward to the correct dose.
The pen can dial up to a maximum of 50 dose steps.
The dose selector changes the number of dose steps.
Only the dose counter and dose pointer will show how many dose steps you select per dose. You can select up to 50 dose steps per dose.



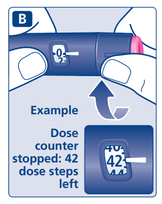
When your pen contains less than 50 dose steps, the dose counter stops at the number of dose steps left. The dose selector clicks differently when turned forward, backward or past the number of dose steps left. Do not count the pen clicks.

Always use the dose counter and the dose pointer to see how many dose steps 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** dose steps are left in your pen. If it shows **less than 50,** the number shown is the number of dose steps left in your pen.

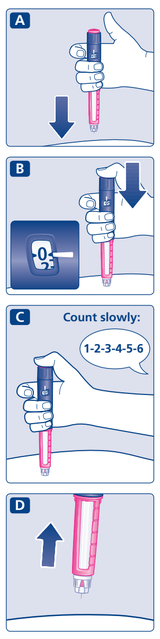


- If you need more medicine than what is left in your pen, you can split your dose between two pens.

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 dose steps 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.

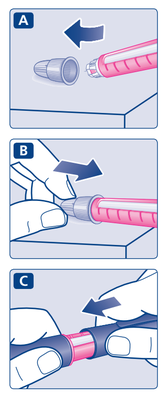
How to identify a blocked or damaged needle?
- If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
- In this case – you have **not** received **any** medicine – even though the dose counter has moved from the original dose 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.