▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

Xultophy® (insulin degludec/liraglutide) solution for injection

1. NAME OF THE MEDICINE

Insulin degludec and liraglutide.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 100 units insulin degludec and 3.6 mg liraglutide.

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

Insulin degludec (rys) and liraglutide (rys) are produced by recombinant DNA technology using *Saccharomyces cerevisiae*.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Xultophy (insulin degludec/liraglutide) is a solution for injection provided in a 3 mL pre-filled multidose disposable pen. Clear, colourless, isotonic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Xultophy is indicated as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, with or without other oral glucose-lowering medicinal products (see Section 5.1 Pharmacodynamic Properties-Clinical trials and Section 4.4 Special Warnings and Precautions for Use' for available data on the different combinations).

4.2 Dose and Method of Administration

Dosage

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

As with all insulin products, adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness. 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 Section 4.4 Special Warnings and Precautions for Use - Hypoglycaemia).

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). 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
Therapy with insulin should be discontinued prior to initiation of Xultophy. When transferring from insulin therapy, the recommended starting dose of Xultophy is 16 dose steps (16 units insulin degludec and 0.6 mg liraglutide) (see Sections 5.1 Pharmacodynamic Properties-Clinical trials and 4.4 Special Warnings and Precautions for Use). 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.

Titration of Xultophy
After starting the recommended starting dose of Xultophy (see Section 4.2 Dose and Method of Administration), titrate the dosage upwards or downwards by two units (see **Table 1**) once weekly or twice weekly (every three to four days), based on the patient's metabolic needs, blood glucose monitoring results, and glycaemic control goal until the desired fasting plasma glucose is achieved.

Table 1 Titration of Xultophy

Pre-breakfast plasma glucose* mmoL/L	**Dose adjustment (twice weekly)** Xultophy (dose steps)
< 4.0	-2
4.0 – 5.0	0
> 5.0	+2

*Self-measured plasma glucose

Other 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 Section 5.2, Pharmacokinetic Properties).

Hepatic impairment

When Xultophy is used in patients with hepatic impairment, glucose monitoring is to be intensified and the dose adjusted on an individual basis (see Section 5.2, Pharmacokinetic Properties).

Paediatric population

Xultophy is not recommended for use in children and adolescents below 18 years of age. No studies have been performed with Xultophy in patients below 18 years of age.

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 sections 4.4 Special Warnings and Precautions for Use and 4.8 Adverse Effects (Undesirable Effects)). For further instructions on administration, see Section 6.6 Special Precautions for Disposal.

Instructions for use and handling

Detailed instruction accompanying the pre-filled pen must be followed. Discard 21 days after first opening. The pre-filled pen is designed to be used with NovoFine® injection needles up to a length of 8 mm and as thin as 32G. Xultophy 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.

Missed dose

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.

4.3 Contraindications

Hypersensitivity to either or both active substances or to any of the excipients listed in Section 6.1 List of Excipients.

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. When Xultophy is used 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 (see Section 4.2 Dose and Method of Administration) of hypoglycaemia and must be advised accordingly. Usual warning symptoms of hypoglycaemia may disappear in patients with long-standing diabetes. As with all products with a basal insulin component, prolonged effect of Xultophy may delay recovery from hypoglycaemia.

Hyperglycaemia

Inadequate dosing and/or discontinuation of antidiabetic treatment may lead to hyperglycaemia and potentially to ketoacidotic 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 thiazolidinediones and insulin medicinal products
Cases of cardiac failure have been reported when thiazolidinediones were 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 thiazolidinediones and Xultophy is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Thiazolidinediones 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. 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. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see Section 4.8 Adverse Effects (Undesirable Effects)).

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 diabetec 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 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.

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.

Use in the elderly
See Section 4.2 Dose and Method of Administration.

Paediatric use
See Section 4.2 Dose and Method of Administration.

Effects on laboratory tests
No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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 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 *assessment of drug-drug interaction*
Liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.

In vivo *assessment of drug-drug interaction*
The delay of gastric emptying caused by liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption of the compounds that were studied, however clinically relevant interactions with other compounds where the effect is dependent on C_{max} and t_{max}, drugs with narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.

Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

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 (Acetaminophen)
Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 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 clinically 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 1.5 h later 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

Effects on fertility
There is no clinical experience with Xultophy with respect to fertility and no animal fertility studies have been performed with insulin degludec and liraglutide in combination. Animal reproduction studies with insulin degludec as a single agent have not revealed any adverse effects on fertility. In a combined fertility and embryofetal study in male and female rats, treatment with subcutaneous doses of insulin degludec up to 21 U/kg/day (yielding 5-6 times the AUC in humans at a dose of 0.8 U/kg/day) prior to mating and in female rats during gestation had no effect on mating performance or fertility. No adverse effects on fertility were observed in male and female rats given subcutaneous doses of liraglutide at ≤1 mg/kg/day, yielding exposure to liraglutide (plasma AUC) 11-13 times higher than that of patients at the maximum recommended human dose.

Women of childbearing potential/contraception in males and females
Because of lack of experience during pregnancy, women of childbearing potential should be advised to discontinue Xultophy if they wish to become pregnant.

Use in pregnancy
Pregnancy Category: B3

There is no clinical experience with use of Xultophy in pregnant women. The potential risk for humans is unknown and therefore Xultophy should not be used during pregnancy. If a patient becomes pregnant, treatment with Xultophy should be discontinued.

No animal embryofetal development studies have been performed with insulin degludec and liraglutide in combination. In rats, treatment with insulin degludec as a single agent at subcutaneous doses ≥13 U/kg/day (resulting in 2.6 times the AUC in humans at a dose of 0.8 U/kg/day) caused an increase in the incidence of fetal skeletal abnormalities. Similar effects were seen with human insulin, and these are probably secondary to maternal hypoglycaemia. No adverse effects on embryofetal development were observed in rabbits at subcutaneous doses up to 3 U/kg/day (resulting in 9 times the human AUC at a dose of 0.8 U/kg/day). Increased embryofetal death and minor fetal skeletal abnormalities (kinked ribs) were observed in rats given liraglutide at 1 mg/kg/day by subcutaneous injection (yielding 11-times the plasma AUC in humans at the maximum recommended clinical dose). In rabbits treated at doses ≥0.01 mg/kg/day (relative exposure, ≥0.2), there was retardation of fetal growth and an increased incidence of several minor skeletal and visceral abnormalities. Postnatal body weight gain was reduced in the offspring of rats treated with liraglutide during gestation and lactation. These findings may have occurred secondary to reduced maternal food consumption. Placental transfer of liraglutide and/or its metabolites was demonstrated in the animal species.

Use in lactation

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. In rats, insulin degludec and its metabolites were secreted in milk; the peak concentration of insulin degludec in milk was less than half of that in plasma. Studies in lactating rats have shown that the transfer of liraglutide and metabolites of close structural relationship into milk was low. Because of lack of experience, Xultophy should not be used during breast-feeding.

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 Adverse Effects (Undesirable Effects)

Summary of the safety profile

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

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

Adverse effects from clinical trials

Tabulated list of adverse events

Table 2 Treatment emergent adverse events (excluding hypoglycaemia*) reported in ≥2% of patients on Xultophy and more frequently than in patients on comparator or placebo

System Organ Class Preferred Term	**Xultophy** **N = 2133** **%**	**Basal Insulins** **N = 1143** **%**	**GLP-1 Receptor Agonists** **N = 557** **%**	**Placebo** **N = 146** **%**
Gastrointestinal disorders				
Nausea	8.3	2.7	17.8	3.4
Diarrhoea	7.4	4.5	13.6	4.8
Vomiting	3.8	1.8	7.5	2.7
Dyspepsia	3.2	0.6	3.9	0.7
Constipation	2.6	0.7	3.8	0.7
Infections and infestations				
Nasopharyngitis	9.0	9.1	13.3	8.2
Upper respiratory tract infection	5.8	5.4	7.4	4.1
Influenza	3.6	3.7	2.5	5.5
Bronchitis	2.5	2.4	2.5	2.7
Sinusitis	2.3	1.2	3.8	2.1
Urinary tract infection	2.1	2.3	4.7	0.7
Investigations				
Lipase increased	6.2	2.8	7.5	4.1
Metabolism and nutrition disorders				
Dyslipidaemia	3.2	3.0	2.7	4.1
Decreased appetite	2.6	0.6	5.4	0
Musculoskeletal and connective tissue disorders				
Arthralgia	3.0	2.4	4.5	2.1
Pain in extremity	2.3	2.3	3.2	1.4
Nervous system disorders				
Headache	8.7	7.1	12.4	5.5
Dizziness	2.2	1.6	4.3	1.4
Respiratory, thoracic and mediastinal disorders				
Cough	2.4	1.9	1.6	0.7

%: percentage of subjects. Trials included: NN9068-3697-main-ext, NN9068-3912, NN9068-3851, NN9068-3951, NN9068-3952 (excluding extension trial), NN9068-4185.
** Hypoglycaemia (System Organ Class: Metabolism and nutrition disorders) was reported in Xultophy with a frequency of 'very common' (≥1/10).*
MedDRA version 22.0

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) and unknown (cannot be estimated from the available data).

Table 3: Adverse reactions reported in phase 3 controlled trials

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	Acquired lipodystrophy
General disorders and administration site conditions	Common	Injection site reaction
	Uncommon	Fatigue
	Unknown	Peripheral oedema (insulin induced)
Investigation	Common	Increased lipase
	Common	Increased amylase
	Uncommon	Increased heart rate

Adverse drug reactions from post-marketing sources

Adverse reactions associated with Xultophy given below are based on post marketing source data, listed by system organ class and frequency.

Table 4: Adverse reactions from post-marketing sources

System Organ Class	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Not known	Cutaneous amyloidosis

Description of selected adverse drug 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.

Allergic reactions

Allergic reactions (manifested with signs and symptoms such as urticaria, rash, pruritus and/or swelling of the face) 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 events including nausea, diarrhoea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, gastroesophageal reflux disease, abdominal distension, eructation, flatulence and decreased appetite have been reported in patients treated with Xultophy. These gastrointestinal adverse events may occur more frequently at the beginning of Xultophy therapy and usually diminish within a few days or weeks on continued treatment.

Injection site reactions

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) have been reported in 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 the risk or prevent these reactions (see section 4.4 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).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 themselves, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

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. 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 blood glucose levels after all meals.

Insulin degludec is a basal insulin that forms soluble multihexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to the ultra-long, flat and stable glucose-lowering effect of insulin degludec with a low day-to-day variability in insulin action.

Insulin degludec binds to the human insulin receptor resulting 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.

The GLP-1 receptor (GLP-1R) is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Liraglutide exhibits 97% homology to human GLP-1. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association (which results in slow absorption), binding to albumin, and enzymatic stability towards the dipeptidyl peptidase (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 may also involve a minor delay in gastric emptying (see Section 4.5, Interactions with Other Medicines and Other Forms of Interactions).

Liraglutide lowers body weight through decreased food intake and loss of predominantly fat mass.

GLP-1 is a physiological regulator of appetite and food intake and GLP-1R is present in several areas of the brain involved in appetite regulation as well as the intestine. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions including the hypothalamus, where liraglutide, via specific activation of the GLP-1R, increased key satiety and decreased key hunger signals.

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 the expression of genes related to inflammation in aortic tissue. In addition, liraglutide had a beneficial effect on plasma lipids, decreasing plasma triglyceride, total cholesterol, LDL and VLDL, and increasing HDL. Liraglutide did not reduce the plaque size of already established plaques.

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.

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 was demonstrated in a 4 hour standardised meal test sub-study in patients uncontrolled on metformin alone or in combination with pioglitazone after 52 weeks treatment.

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

The effect of liraglutide on cardiac repolarisation was tested in a QTc study. Liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation. For insulin degludec, no statistically significant difference was observed between insulin degludec and comparator in change from baseline in QTc intervals based on ECG analysis from a 12-month clinical trial.

Clinical trials
Improvement of glycaemic control, prevention of microvascular complications and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes. 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 basal bolus insulin therapies. The trials were of 26 weeks' duration with one study further extended to 52 weeks. A total of 4432 patients were randomised. In all trials, a twice weekly titration regimen for Xultophy was used (see **Table 1**). 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 haemoglobin A1c (HbA_{1c}), whereas one study demonstrated a similar reduction of HbA_{1c} in both treatment arms.

Large cardiovascular outcomes trials were conducted with liraglutide (the LEADER trial) and insulin degludec (the DEVOTE trial), monocomponents of Xultophy. The LEADER trial included 9,340 patients with type 2 diabetes mellitus at high cardiovascular risk and the DEVOTE trial included 7,637 patients with type 2 diabetes mellitus at high cardiovascular risk.

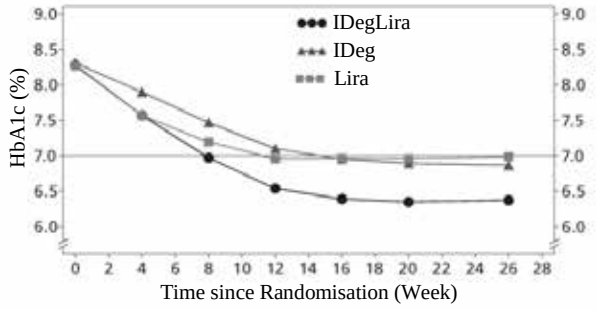
Glycaemic control
Add-on to metformin alone or in combination with pioglitazone - Xultophy compared to insulin degludec and liraglutide (Trial 3697)
The efficacy and safety of Xultophy compared to insulin degludec and liraglutide, all once-daily, were studied in a 26-week randomised, controlled, open-label, 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 and 10 units, respectively, and the dose was titrated twice weekly according to **Table 1**. 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

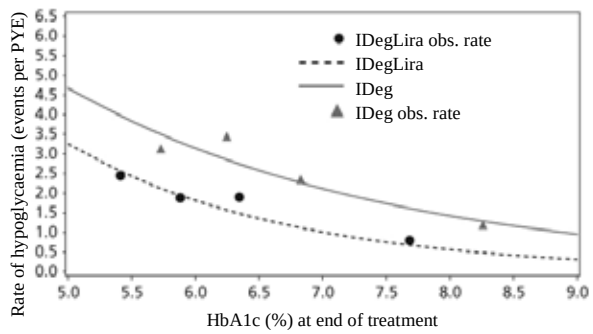
until the maintenance dose of 1.8 mg was reached. The maximum dose of Xultophy was 50 dose steps, while there was no maximum dose in the insulin degludec arm.

The reduction in HbA_{1c} from baseline to 26 weeks was 1.9% with Xultophy, showing superiority to liraglutide (estimated treatment difference -0.64%, p<0.0001) and noninferiority compared to insulin degludec (estimated treatment difference -0.47%, p<0.0001). Body weight was reduced by 0.5 kg with Xultophy with an estimated treatment difference between Xultophy and insulin degludec of -2.22 kg (p<0.0001), confirming superiority compared to insulin degludec. Xultophy showed a statistically significant reduction in overall risk of hypoglycaemia compared to insulin degludec, confirming superiority compared to insulin degludec (p=0.0023). As depicted in **Figure 1**, patients experienced lower rates of hypoglycaemia with Xultophy irrespective of glycaemic control as compared to insulin degludec.

After 26 weeks of treatment, 60.4% of patients treated with Xultophy reached a target of HbA_{1c} <7% without confirmed hypoglycaemic episodes. 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**.The key results of the trial are presented in **Figure 1**, **Figure 2** and **Figure 3**.

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





The curves are mean hypo rates from a negative binomial model with unique treatment trajectories and the symbols are observed hypo rates vs. mean HbA1c by quartiles.

IDegLira=Xultophy, IDeg=insulin degludec, Lira=liraglutide, obs. rate=observed rate, PYE=patient year of exposure
*Confirmed hypoglycaemia is defined as severe hypoglycaemia (episode requiring assistance of another person) and/or minor hypoglycaemia (plasma glucose <3.1 mmol/L irrespectively of symptoms).

Figure 2: Mean change in body weight by treatment week in patients inadequately controlled on metformin alone or in combination with pioglitazone

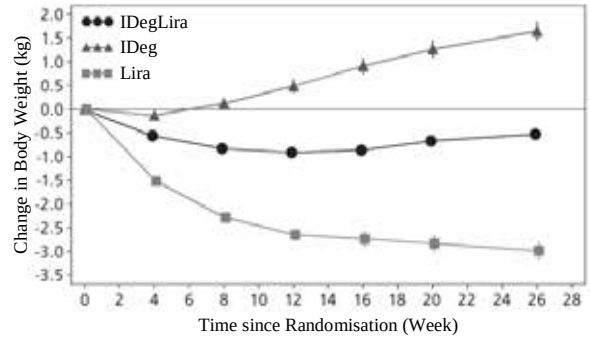
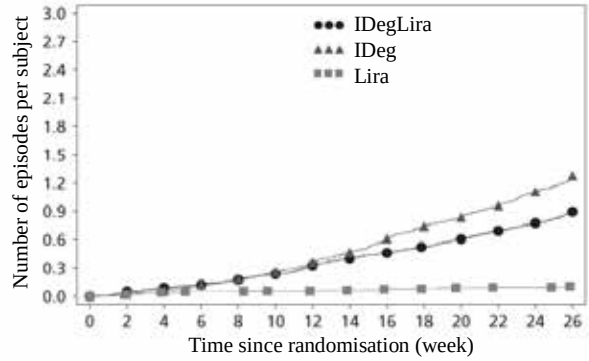


Figure 3: Mean cumulative number of confirmed hypoglycaemic* episodes in patients inadequately controlled on metformin alone or in combination with pioglitazone.



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

The rate per patient year of exposure 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.

Add-on to metformin alone or in combination with pioglitazone – 52-week data: Xultophy compared to insulin degludec and liraglutide (Trial 3697-ext)
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 - Xultophy compared to placebo (Trial 3951)

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, and the dose was titrated twice weekly. Titration was performed as outlined in **Table 1** though with a titration target of 4–6 mmol/L.

The reduction in HbA_{1c} from baseline to 26 weeks was 1.45% with Xultophy, showing superiority to placebo (estimated treatment difference -1.02%, p<0.0001). Body weight was increased by 0.5 kg with Xultophy with an estimated treatment difference between Xultophy and placebo of 1.48 kg (p<0.0001).

The key results of the trial are presented in **Figure 4**, **Figure 5** and **Figure 6**.

Figure 4: Mean HbA_{1c} (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on sulfonylurea alone or in combination with metformin

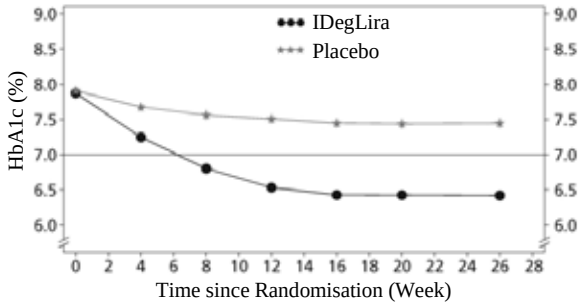


Figure 5: Mean change in body weight by treatment week in patients inadequately controlled on sulfonylurea alone or in combination with metformin

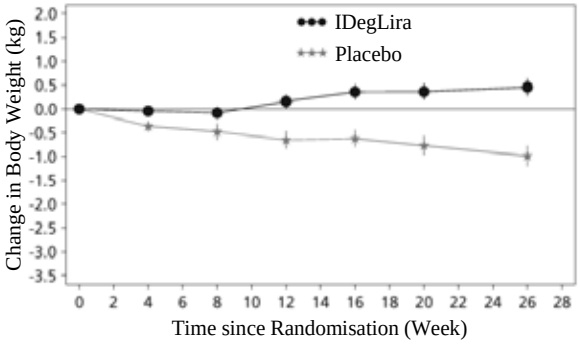
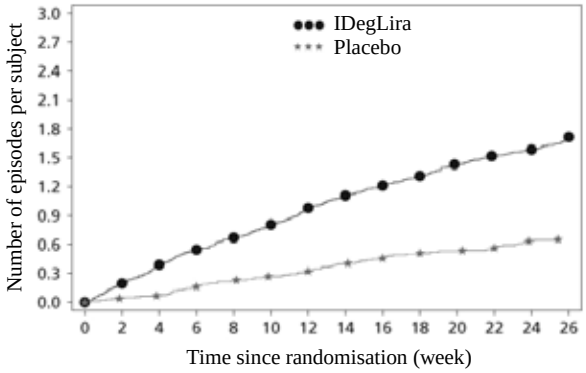


Figure 6: Mean cumulative number of hypoglycaemic episodes in patients inadequately controlled on sulfonylurea alone or in combination with metformin



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

Add-on to SGLT2i alone or in combination with metformin - Xultophy compared to insulin glargine U100 (Trial 4229)

In an open label trial comparing the efficacy and safety of Xultophy and insulin glargine U100, 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. Adding Xultophy to SGLT2i ± OAD resulted in 42.1% of patients reaching HbA_{1c} target <7% without severe or blood-glucose confirmed symptomatic hypoglycaemic episodes and without weight gain compared to 16.8% of patients treated with insulin glargine added to SGLT2i ± OAD (odds ratio 3.36, [2.09; 5.41]). Safety results from the trial were comparable to the known safety profile of Xultophy.

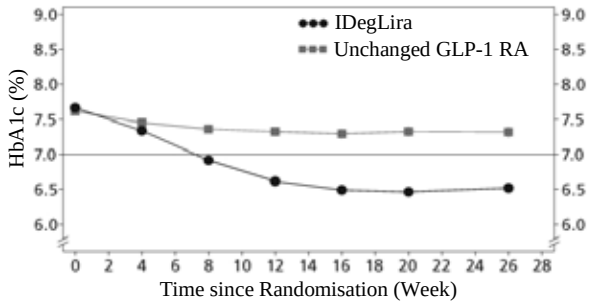
Transfer from GLP-1 receptor agonist therapy - Xultophy compared to GLP-1 receptor agonist therapy (Trial 3851):

The efficacy and safety of Xultophy (once-daily) compared to unchanged GLP-1 receptor agonist therapy, were studied in a 26-weeks randomised, open-label, treat-to-target trial in patients with type 2 diabetes mellitus inadequately controlled on a maximum approved or tolerated dose of 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 1**. Patients in the GLP-1 receptor agonist arm were to continue pretrial GLP-1 receptor agonist treatment. The reduction in HbA_{1c} from baseline to

26 weeks was 1.3% with Xultophy, showing superiority compared to unchanged GLP-1 receptor agonist (estimated treatment difference -0.94, p<0.001).

The key results of the trial are presented in **Figure 7**.

Figure 7: Mean HbA_{1c} (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on GLP-1 receptor agonists



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

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 insulin glargine U100 - Xultophy compared to basal-bolus insulin regimen (Trial 4185):

The efficacy and safety of Xultophy compared to a basal-bolus insulin regimen consisting of insulin glargine U100 in combination with prandial insulin aspart at main meals, 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 U100 (20–50 units) and metformin. The starting dose of Xultophy was 16 dose steps. In the basal-bolus arm, the starting dose of insulin glargine U100 was equal to the pretrial daily dose and the starting dose of prandial insulin aspart was 4 units before main meals. The dose of Xultophy and insulin glargine U100 was titrated twice weekly according to **Table 1**, whereas prandial insulin aspart was titrated twice weekly based on preprandial and bedtime self-measured plasma glucose (SMPG) obtained on the three previous days. The maximum daily dose was 50 dose steps for Xultophy, while there was no maximum dose for insulin glargine U100 and insulin aspart.

The reduction in HbA_{1c} from baseline to 26 weeks was -1.5% with Xultophy and -1.5% with basal-bolus regimen, confirming noninferiority of Xultophy compared to basal-bolus regimen (estimated treatment difference -0.02, p<0.0001). The overall rate of severe or blood glucose confirmed symptomatic hypoglycaemia was lower with Xultophy compared to basal-bolus regimen (estimated treatment ratio 0.11, p<0.0001), confirming superiority compared to basal-bolus regimen. Body weight was reduced by -0.9 kg with Xultophy and increased by 2.6 kg with basal-bolus regimen with an estimated treatment difference between Xultophy and basal-bolus regimen of -3.57 kg, confirming superiority of Xultophy compared to basal-bolus regimen (p<0.0001).

After 26 weeks of treatment, there was no statistically significant difference in FPG between Xultophy and basal-bolus regimen.

Daily dose of the insulin degludec component of Xultophy after 26 weeks of treatment was statistically significantly lower compared to basal insulin dose in the basal-bolus arm (40 units vs 52 units, p<0.0001) and statistically significantly lower compared to total insulin dose in the basal-bolus arm (40 units vs 84 units).

Daily dose of the insulin degludec component of Xultophy after 26 weeks of treatment was statistically significantly lower compared to basal insulin dose in the basal-bolus arm (40 units vs 52 units, p<0.0001) and statistically significantly lower compared to total insulin dose in the basal-bolus arm (40 units vs 84 units, p<0.0001).

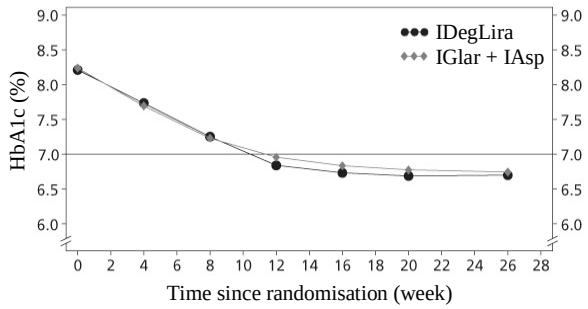
After 26 weeks of treatment with Xultophy, 57.6% of patients reached the HbA_{1c} target of <7% without severe or blood glucose confirmed symptomatic hypoglycaemic episodes compared to basal-bolus regimen (33.5%). The estimated odds of reaching target was statistically significantly higher for Xultophy compared to basal-bolus regimen (p<0.0001).

The rate per patient year of exposure of severe hypoglycaemia was 0.02 (3 patients out of 252) for Xultophy and 0.08 (4 patients out of 253) for basal-bolus regimen.

The rate of nocturnal severe or blood glucose confirmed symptomatic hypoglycaemia was statistically significantly lower with Xultophy compared to basal-bolus regimen (estimated treatment ratio 0.08, p<0.0001).

The key results of the trial are presented in **Figure 8**, **Figure 9** and **Figure 10**.

Figure 8: Mean HbA_{1c} (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine U100



IDegLira=Xultophy, IGlar + IAsp = insulin glargine U100 + insulin aspart

Figure 9: Mean cumulative number of severe or blood glucose confirmed symptomatic hypoglycaemic episodes in patients inadequately controlled on insulin glargine U100

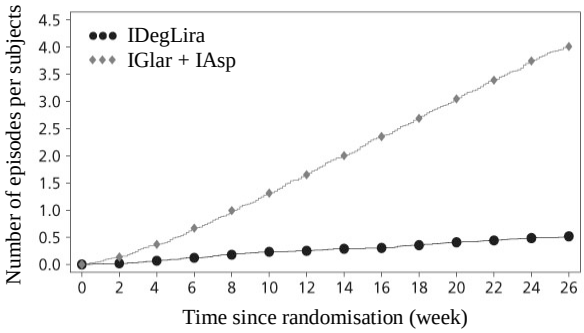
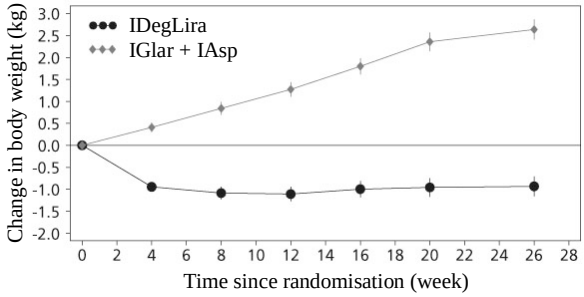


Figure 10: LSMean change in body weight by treatment week in patients inadequately controlled on insulin glargine U100



Transfer from insulin glargine - Xultophy compared to insulin glargine U100 (Trial 3952)
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 for insulin glargine the starting dose was equal to the pretrial daily dose. The dose was titrated twice weekly according to **Table 1**. The maximum allowed dose was 50 dose steps for Xultophy, while there was no maximum dose for insulin glargine.

The reduction in HbA_{1c} from baseline to 26 weeks was 1.8% with Xultophy and 1.1% with insulin glargine, confirming superiority of Xultophy compared to insulin glargine (estimated treatment difference -0.59, $p<0.001$). Body weight was reduced by 1.4 kg with Xultophy and increased by 1.8 kg with insulin glargine with an estimated treatment difference between Xultophy and insulin glargine of -3.20 kg, confirming superiority of Xultophy compared to insulin glargine ($p<0.001$).

After 26 weeks of treatment, there was no statistically significant difference in FPG between Xultophy and insulin glargine. Daily dose of the insulin degludec component of Xultophy after 26 weeks of treatment was statistically significantly lower for Xultophy compared to the insulin glargine dose (41 units vs 66 units, $p<0.001$), resulting in an insulin sparring effect of Xultophy.

The overall rate of hypoglycaemia was lower with Xultophy compared to insulin glargine (estimated treatment ratio 0.43, p<0.001), confirming superiority compared to insulin glargine.

After 26 weeks of treatment, 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 rate per patient year of exposure 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 hypoglycaemia was statistically significantly lower with Xultophy compared to insulin glargine (estimated treatment ratio 0.17, p<0.001).

Xultophy significantly improved overall physical health and diabetes management and significantly reduced treatment burden compared to insulin glargine.

The key results of the trial are presented in **Figure 11**, **Figure 12** and **Figure 13**

Figure 11: Mean HbA_{1c} (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine

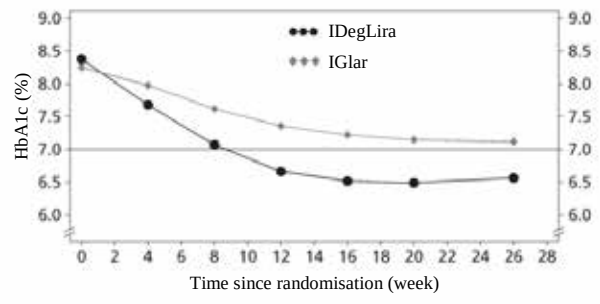


Figure 12: Mean change in body weight by treatment week in patients inadequately controlled on insulin glargine

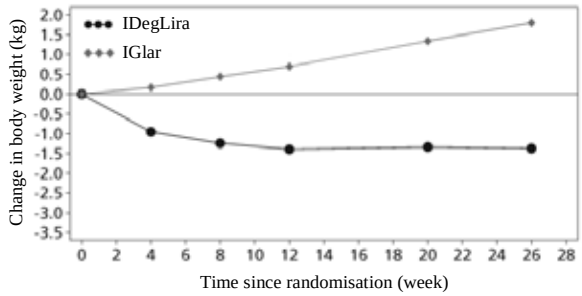
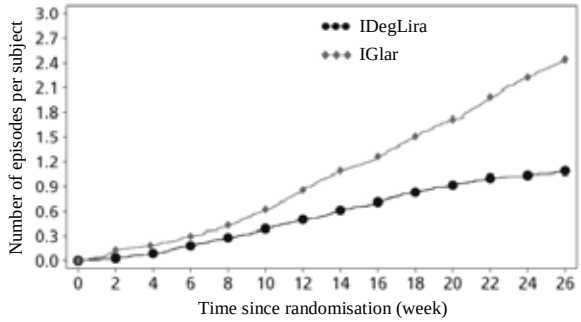


Figure 13: Mean cumulative number of hypoglycaemic episodes in patients inadequately controlled on insulin glargine



Transfer from basal insulin therapies - Xultophy compared to insulin degludec (Trial 3912)
The efficacy and safety of Xultophy compared to insulin degludec, both once-daily, were studied in a 26-week, 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 and 16 units, respectively, and the dose was titrated twice weekly according to **Table 1** above. The maximum allowed dose was 50 dose steps for Xultophy and 50 units for insulin degludec.

The reduction in HbA_{1c} from baseline to end of trial was 1.9% with Xultophy, showing superiority compared to insulin degludec at a maximum insulin degludec dose of 50 units (estimated treatment difference -1.05%, $p<0.0001$). Body weight was reduced by 2.7 kg with Xultophy showing a statistically significant reduction compared to insulin degludec (estimated treatment difference -2.51 kg, $p<0.0001$), and the overall risk of hypoglycaemia was similar with Xultophy and insulin degludec despite statistically significantly lower end of trial HbA_{1c} with Xultophy.

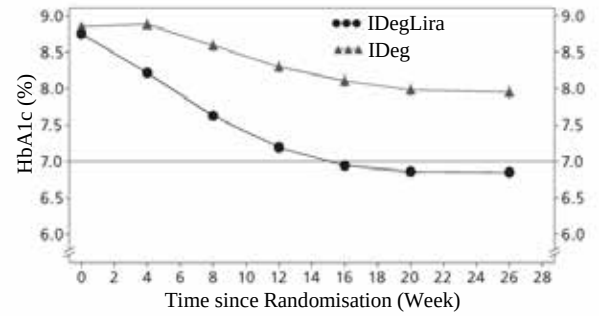
After 26 weeks of treatment, 48.7% of patients treated with Xultophy reached the HbA_{1c} target of <7% without confirmed hypoglycaemic episodes compared to 15.6% treated with insulin degludec (odds ratio 5.57, $p<0.0001$).

The rate per patient year of exposure 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.

The key results are presented in **Figure 14**, **Figure 15** and **Figure 16**.

Figure 14: Mean HbA_{1c} (%) by treatment week in patients with type 2 diabetes mellitus inadequately controlled on basal insulin



IDegLira=Xultophy, IDeg=insulin degludec

Figure 15: Mean change in body weight by treatment week in patients inadequately controlled on basal insulin

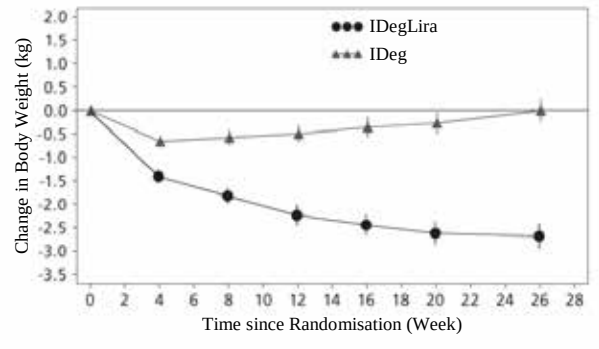
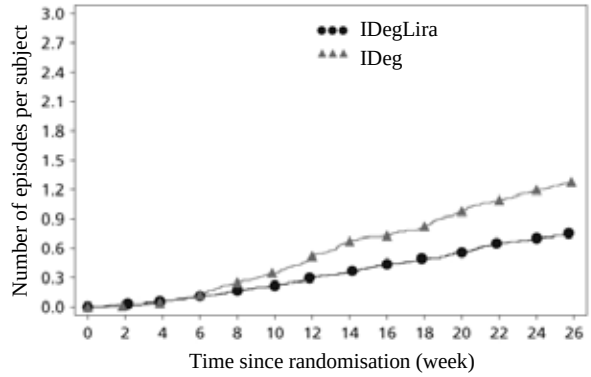


Figure 16: Mean cumulative number of hypoglycaemic episodes in patients inadequately controlled on basal insulin



Cardiovascular evaluation

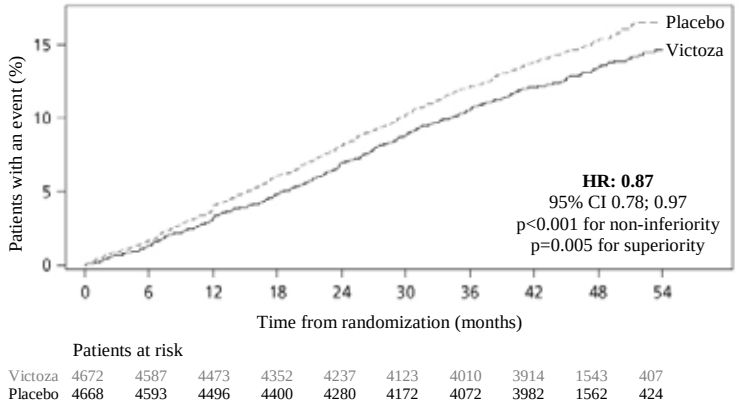
Liraglutide (Victoza®)

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 managing HbA_{1c} and cardiovascular (CV) risk factors. Patients had type 2 diabetes and were anti-diabetic medication naïve or treated with one or more OADs or insulin (human NPH insulin, long-acting insulin or premixed insulin – either

alone or in combination with OAD(s)) - at baseline (SOC). Patients were also at high risk of cardiovascular events, defined as either 50 years of age and with concomitant cardiovascular, cerebrovascular, peripheral vascular disease, chronic renal failure or chronic heart failure, or 60 years of age and other specified risk factors of vascular disease.

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 significantly reduced the risk of MACE vs placebo with an estimated hazard ratio [95% CI] of 0.87 [0.78, 0.97] (p=0.005), corresponding to a relative risk reduction of 13% (**Figure 17**). The number of subjects that needed to be treated with liraglutide for 3 years to prevent the first MACE was 66. The estimated hazard ratio (HR) was consistently below 1 for all 3 MACE components.

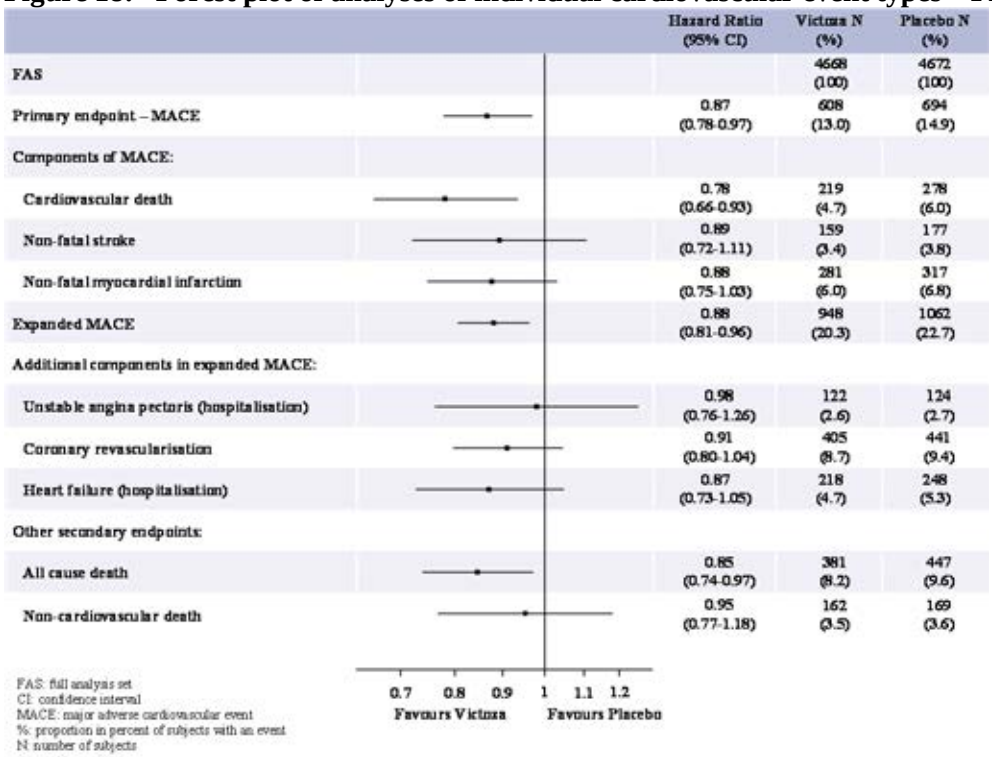
Figure 17: Kaplan Meier plot of time to first MACE – Full analysis set (FAS) population



FAS: full analysis set.

Liraglutide also significantly reduced the time to first expanded MACE (primary MACE, unstable angina pectoris leading to hospitalisation, coronary revascularisation, or hospitalisation due to heart failure) and other secondary endpoints (**Figure 18**).

Figure 18: Forest plot of analyses of individual cardiovascular event types – FAS population

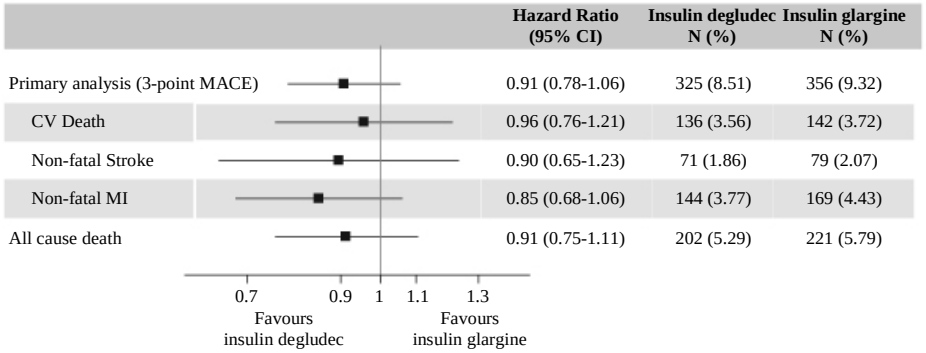


Insulin degludec (Tresiba®)

DEVOTE was a randomised, double-blind, active-controlled, treat-to-target and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of Tresiba versus insulin glargine (100 units/mL) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events. Patients eligible to enter the trial were 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure (85% of the enrolled population) or were 60 years of age or older and had other specified risk factors for cardiovascular disease (15% of the enrolled population).

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 of MACE comparing Tresiba to insulin glargine. The cardiovascular safety of Tresiba as compared to insulin glargine was confirmed (**Figure 19**).

Figure 19: Forest plot of analysis of the composite 3-point MACE and individual cardiovascular endpoints in DEVOTE



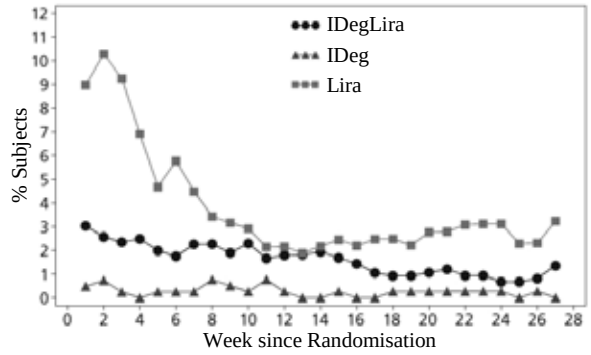
N: Number of subjects with a first EAC confirmed event during trial. %: Percentage of subjects with a first EAC confirmed event relative to the number of randomised subjects. EAC: Event adjudication committee. CV: Cardiovascular. MI: Myocardial infarction. CI: 95% confidence interval.

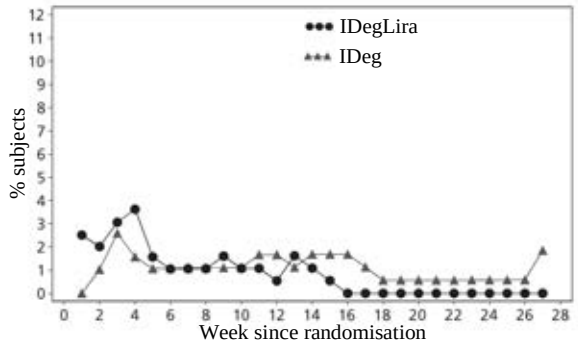
At baseline, HbA_{1c} was 8.4% in both treatment groups and after 2 years HbA_{1c} was 7.5% both with insulin degludec and insulin glargine.

Nausea

The proportion of patients reporting nausea at any point during treatment with Xultophy was below 4%, see **Figure 20**, and was transient in nature for most patients.

Figure 20: Percentage of patients with nausea by treatment week in patients inadequately controlled on metformin alone or in combination with pioglitazone (upper) and in patients inadequately controlled on basal insulin (lower)





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 patients inadequately controlled on GLP-1 receptor agonists, systolic blood pressure was reduced by 0.6 mmHg with Xultophy and 0.5 mmHg with continued GLP-1 receptor agonist therapy, respectively. The difference was not statistically significant. In three trials with patients inadequately controlled on basal insulin, systolic blood pressure was reduced by 5.4 mmHg with Xultophy vs 1.7 mmHg with insulin degludec, with a statistically significant estimated treatment difference of -3.71 mmHg (p=0.0028) (Trial 3912), 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) (Trial 3952) 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) (Trial 4185).

Microvascular evaluation

In the LEADER trial, microvascular events comprised nephropathy and retinopathy outcomes. The analysis of time to first microvascular event for liraglutide vs placebo had a HR of 0.84 [0.73, 0.97]. The HR for liraglutide vs placebo was 0.78 [0.67, 0.92] for time to first nephropathy event and 1.15 [0.87, 1.52] for time to first retinopathy event.

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 protein (>99% and >98%, respectively).

Metabolism
Insulin degludec
Degradation of insulin degludec is similar to that of human insulin.

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

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

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

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 patients with different ethnic origins.

Renal impairment
Insulin degludec

There are no differences in the pharmacokinetics of insulin degludec between healthy subjects and patients with renal impairment following a single dose.

Liraglutide
Liraglutide exposure was mildly reduced in subjects with renal impairment compared to individuals with normal renal function in a single-dose trial. Liraglutide exposure was lowered by 33%, 14%, 27% and 26%, respectively, in subjects 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.

Hepatic impairment
Insulin degludec
There are no differences in the pharmacokinetics of insulin degludec between healthy subjects and patients with hepatic impairment following a single dose.

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

5.3 Preclinical Safety Data

Genotoxicity
Genotoxicity studies have not been carried out with insulin degludec. Liraglutide was not mutagenic in the bacterial Ames assay, and not clastogenic in human lymphocytes *in vitro*, or in rat lymphocytes and bone marrow *in vivo*.

Carcinogenicity
No animal carcinogenicity studies have been performed with insulin degludec and liraglutide in combination. Data for the individual agents are described below.

Insulin degludec
Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin degludec. In a 52-week study, rats received subcutaneous doses of insulin degludec up to 10 U/kg/day (resulting in 5 times the AUC in humans at a dose of 0.8 U/kg/day). No treatment-related increases in incidences of hyperplasia, benign or malignant tumours were recorded, and no treatment related changes in the female mammary gland cell proliferation were found using BrdU incorporation. *In vitro* studies showed the ratio of mitogenic relative to metabolic potency for insulin degludec is unchanged compared to human insulin

Liraglutide

Liraglutide caused thyroid C-cell adenomas and carcinomas in two-year studies in mice and rats. C-cell neoplasia was observed in mice at subcutaneous doses ≥1 mg/kg/day (relative exposure based on plasma AUC, ≥7.7) and in rats at all doses tested (≥0.075 mg/kg/day subcutaneously; relative exposure, ≥0.5). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day subcutaneously; relative exposure, ≤64). The findings in mice and rats are mediated by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot presently be completely excluded.

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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 below 30°C or in a refrigerator (2°C – 8°C) for up to 21 days. Do not freeze. Keep the cap on the pre-filled pen in order to protect from light. Protect from heat.

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 and 5 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy. The patient should discard the needle after each injection.

6.7 Physicochemical Properties

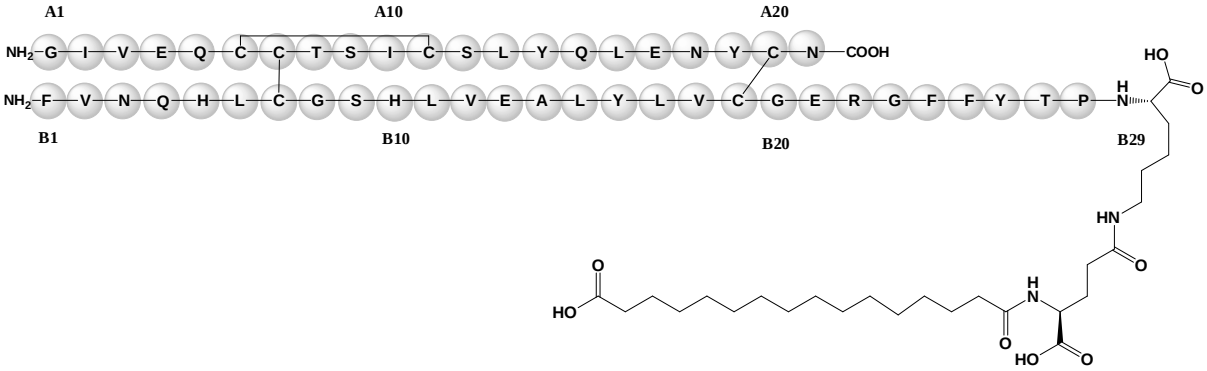
Chemical structure

Insulin degludec

Molecular formula: $C_{274}H_{411}N_{65}O_{81}S_6$

Molecular weight: 6103.97 daltons

Structural formula:

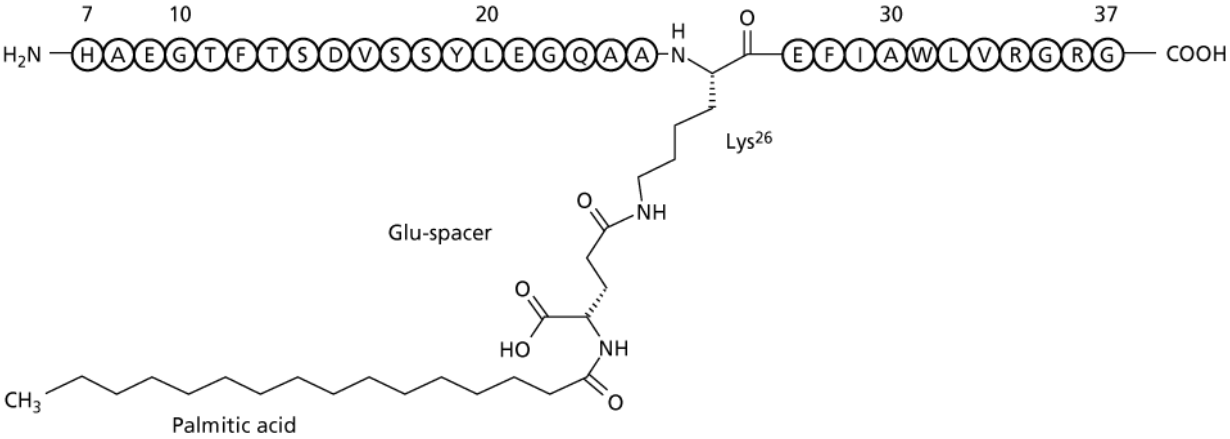


Liraglutide

Molecular formula: $C_{172}H_{265}N_{43}O_{51}$

Molecular weight: 3751.20 daltons

Structural formula:



CAS number

Insulin degludec

844439-96-9

Liraglutide
204656-20-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 3, 21 Solent Circuit,
Baulkham Hills,
NSW 2153,
Australia.

http://www.novonordisk.com.au

9. DATE OF FIRST APPROVAL

17 December 2020

10. DATE OF REVISION

Summary table of changes

Section changed	Summary of new information