



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for insulin degludec/liraglutide

Proprietary Product Name: Xultophy

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

March 2021

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AIHW	Australian Institute of Health and Welfare
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific Annex
CI	Confidence interval
CMI	Consumer Medicines Information
CPD	Certified Product Details
DDP-4	Dipeptidyl peptidase-4
DLP	Data lock point
EU	European Union
FPG	Fasting plasma glucose
GLP-1	Glucagon like peptide-1
GLP-1R	Glucagon like peptide-1 receptor
GMP	Good Manufacturing Practice
HbA1c	Glycated haemoglobin
HCP	Healthcare Professional
IAsp	Insulin aspart
IDeg	Insulin degludec
IGlar	Insulin glargine
ISO	International Organization for Standardization
Lira	Liraglutide
PDS290	Pre-filled pen device for Xultophy
PI	Product Information
PK	Pharmacokinetic(s)

Abbreviation	Meaning
PSUR	Periodic safety update report
RMP	Risk management plan
SC	Subcutaneous
SE	Standard Error
SMPG	Self measured plasma glucose
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
US(A)	United States (of America)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New combination of active ingredients
<i>Product name:</i>	Xultophy
<i>Active ingredients:</i>	Insulin degludec, liraglutide
<i>Decision:</i>	Approved
<i>Date of decision:</i>	17 December 2020
<i>Date of entry onto ARTG:</i>	22 December 2020
<i>ARTG number:</i>	328580
<i>, Black Triangle Scheme:¹</i>	<p>Yes</p> <p>This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia</p>
<i>Sponsor's name and address:</i>	<p>Novo Nordisk Pharmaceuticals Pty Ltd</p> <p>PO Box 7586</p> <p>Baulkham Hills, NSW, 2153</p>
<i>Dose form:</i>	Solution for injection (subcutaneous)
<i>Strength:</i>	<p>Insulin degludec: 100 units/mL</p> <p>Liraglutide: 3.6 mg/mL</p>
<i>Container:</i>	Pre-filled pen
<i>Pack sizes:</i>	Packs of 1, 3, and 5 x 3 mL pre-filled pen(s)
<i>Approved therapeutic use:</i>	<p><i>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).</i></p>
<i>Route of administration:</i>	Subcutaneous

¹ The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

<i>Dosage:</i>	<p>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.</p> <p>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</p> <p>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.</p> <p>The recommended starting dose of Xultophy is 10 dose steps (10 units insulin degludec and 0.36 mg liraglutide).</p> <p>Particular information regarding add-on to oral glucose lowering medicinal products (including sulfonylurea therapy), transfer from GLP-1 receptor agonists, transfers from insulin regimes and titration are listed in the Product Information.</p> <p>For further information regarding dosage, refer to the Product Information.</p>
<i>Pregnancy category:</i>	<p>Category B3</p> <p>Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.</p> <p>Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.</p> <p>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.</p>

Product background

This AusPAR describes the application by Novo Nordisk Pharmaceuticals Pty Ltd (the sponsor) to register Xultophy (insulin degludec 100 units/mL liraglutide 3.6 mg/mL) solution for injection pre-filled pen 3 mL for the following proposed indication:

Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with one or more 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).

In patients where it is indicated to improve glycaemic control, liraglutide, a component of Xultophy, is indicated to reduce the risk of cardiovascular events in those at high cardiovascular risk, as an adjunct to standard of care therapy (see Section 5.1 Pharmacodynamic Properties-Clinical trials). However, the effectiveness of Xultophy on reducing the risk of cardiovascular events in adults with type 2 diabetes mellitus has not been established.

The proposed drug product Xultophy, involves a novel drug combination of two active ingredients, insulin degludec and liraglutide, both approved in Australia and used in the treatment of diabetes.

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is one of the hormones that regulates blood sugar concentrations. Insulin interacts with insulin receptors to reduce blood glucose concentrations.

Type 2 diabetes (T2DM), formerly called non-insulin-dependent, or adult-onset, results from the body's ineffective use of insulin. Type 2 diabetes comprises the majority of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity.

Diabetes has long term complications due primarily to microangiopathy. These include retinopathy, nephropathy, coronary vascular disease, peripheral neuropathy and peripheral vascular disease. The risk of developing these complications increases with the duration of the illness, and with poor control of blood glucose concentrations.

The prevalence of T2DM in Australia is reported by the Australian Institute of Health and Welfare (AIHW 2019) as:

'An estimated 1 million Australian adults (5%) had type 2 diabetes in 2017–18, according to self-reported data from the ABS² 2017–18 National Health Survey. Proportions were:

- Slightly higher for men than women (6% and 4%). Age-specific rates for males were higher than females from age 45 years onwards.
- Relatively similar across Major cities (5%), Inner regional (4%) and Outer regional and Remote areas (6%).
- Around twice as high in the lowest socioeconomic group (7%) compared with the highest socioeconomic group (3%).

Information based on self-reported data only is likely to underestimate the prevalence of type 2 diabetes as many cases remain unreported, due to survey participants either not knowing or accurately reporting their diabetes status.'

Current treatment options

The first line treatment of T2DM is through changes to diet and exercise. If this is not successful, metformin is recommended. If metformin is neither tolerated nor successful, other treatment options include sulphonylureas (SU), dipeptidyl peptidase-4 inhibitors (DDP-4 inhibitors, or 'gliptins'), pioglitazone, insulin, glucagon like peptide 1 (GLP-1)

² ABS = Australian Bureau of Statistics.

agonists and SGLT-2 inhibitors (or 'gliflozins'). Clinical practice guidelines now recommend a patient orientated approach to the choice of medications after metformin.

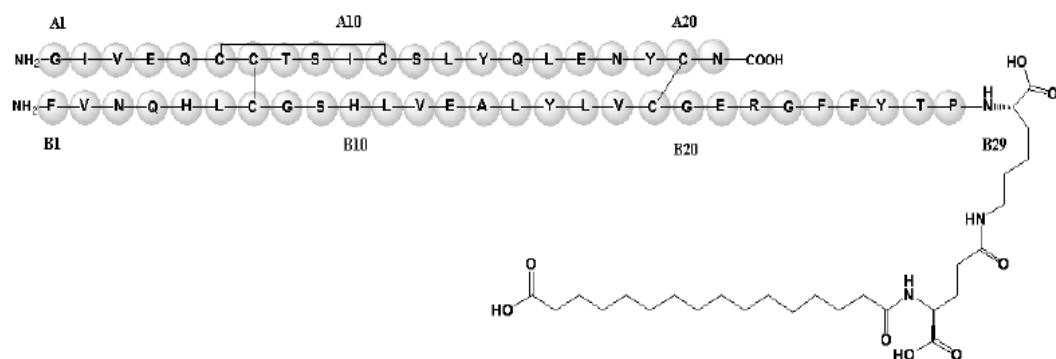
It is not uncommon for patients with long standing diabetes to be on multiple medications for optimal glycaemic control.

The proposed drug product, Xultophy, incorporates two drugs already approved for the treatment of T2DM in Australia.

Insulin degludec

Insulin degludec is an ultra-long acting basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed. Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has been omitted and a side chain consisting of glutamic acid and a C16 fatty acid has been attached (chemical name: LysB29($\text{N}\varepsilon$ -hexadecanediyl- γ -Glu) des(B30) human insulin). Insulin degludec is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. It has the following chemical structure. The molecular structure of insulin degludec is represented in Figure 1.

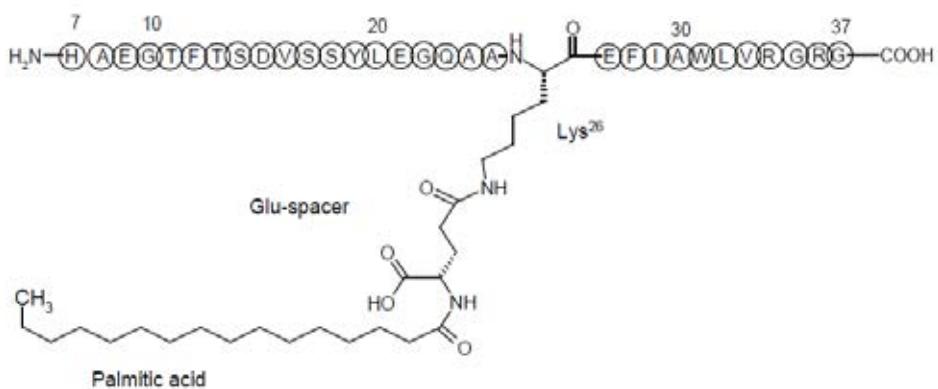
Figure 1: Insulin degludec molecular structure



Liraglutide

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor (GLP-1R). Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26. It has the following molecular structure, as shown in Figure 2.

Figure 2: Liraglutide molecular structure



Regulatory status

For Australian regulatory purposes, this product is considered a new drug combination of two currently approved drugs used in the treatment of T2DM.

Insulin degludec is an ultra-long acting basal insulin. It was first listed on the Australian Register of Therapeutic Goods (ARTG) on 29 November 2017 in the form of the products Tresiba FlexTouch and Tresiba Penfill.³ The currently approved indication is:⁴

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year

Liraglutide is a human GLP analogue that binds to and activates the GLP-1R. It is registered as Victoza (as a 1.2 mg or 1.8 mg dose for the treatment of diabetes) and as Saxenda (as a 3.0 mg dose for obesity). Liraglutide (as Victoza) was first registered on the ARTG in August 2010.⁵

The currently approved indication for Victoza (1.2 mg and 1.8 mg doses) is:

Glycaemic control

Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

- *as monotherapy when metformin is contraindicated or is not tolerated*
- *in combination with other glucose lowering medicines.*

Prevention of cardiovascular events

In patients where Victoza is indicated to improve glycaemic control, Victoza is indicated to reduce the risk of cardiovascular events in those at high cardiovascular risk, as an adjunct to standard of care therapy (see section 5.1 Pharmacodynamic Properties-Clinical Trials)

International regulatory status

At the time the TGA considered this application, similar applications had been approved as shown in Table 1, below.

Table 1: International regulatory status

Region	Status	Approved indications
European Union (EU)	18 September 2014 (Initial authorisation) 25 June 2015 (Extension of indication to include the transfer of patients from Glucagon-Like peptide-1 (GLP1) receptor agonist (RA) treatment to Xultophy.)	<i>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</i>

³ AusPAR Tresiba FlexTouch/Penfill insulin degludec (rys) Novo Nordisk Pharmaceuticals Pty Ltd PM-2016-02721-1-5. Available at: <https://www.tga.gov.au/auspar/auspar-insulin-degludec-rys>

⁴ ARTG record for Tresiba FlexTouch and Tresiba Penfill, ARTG record number 280302, 280301 and 280300.

⁵ AusPAR Victoza/Saxenda liraglutide Novo Nordisk Pharmaceuticals Pty. Ltd. - PM-2016-003931-1-5. Available at: <https://www.tga.gov.au/auspar/auspar-liraglutide-0>

Region	Status	Approved indications
	7 June 2018 (Rewording of the indication, but indication scope unchanged).	<i>studied, see sections 4.4, 4.5 and 5.1</i>
United States of America (USA)	21 November 2016 (initial New Drug Application) 28 February 2019 (Extension of indication to include addon to oral antidiabetic drugs (OADs), simplification of indication wording	<i>Xultophy 100/3.6 is a combination of insulin degludec, a long-acting human insulin analog, and liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.</i>
Canada	11 April 2018 (Initial registration)	<i>Xultophy is indicated as an adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily), do not provide adequate glycemic control.</i>
Switzerland	12 September 2014 (initial registration) 3 September 2019 (Addition of text on cardiovascular event prevention for liraglutide in indication text)	<i>Xultophy is used in combination with other blood glucose lowering medicines in adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (for study results on the combination investigated in clinical studies with respect to combinations as well as effects, see section 'Properties/Efficacy').</i> <i>Liraglutide, a component of Xultophy, is indicated for the prevention of cardiovascular events in patients with type 2 diabetes mellitus and already manifested cardiovascular disease (see section 'Clinical efficacy'). The effectiveness of Xultophy on reducing the risk of cardiovascular events in adults with type 2 diabetes mellitus has not been established.</i>

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-05122-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2020
First round evaluation completed	1 July 2020
Sponsor provides responses on questions raised in first round evaluation	20 August 2020
Second round evaluation completed	15 October 2020
Delegate's Overall benefit-risk assessment	29 October 2020
Registration decision (Outcome)	17 December 2020
Completion of administrative activities and registration on the ARTG	22 December 2020
Number of working days from submission dossier acceptance to registration decision*	186 days

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There were no objections on quality grounds for the approval of Xultophy, pending the issue of Good Manufacturing Practice (GMP) clearance of one of the sites of manufacture.

The PDS290 IDegLira pen-injector is a pen-shaped, prefilled device containing a 3 mL cartridge with the drug product. The PDS290 IDegLira pen-injector is designed and developed by the sponsor (Novo Nordisk A/S) to comply with the relevant requirements of Annex I 'Essential Requirements' of Directive 93/42 EEC.⁶ The drug is not in contact

⁶ Directive 93/42/EEC, Annex I of 14 June 1993 concerning medical devices, is a European Medical Device Directive – Essential Requirements Checklist, applicable in Australia.

with the device. The device is intended to function with a standard needle thread or a needle with a bayonet coupling.

The results of dose accuracy test of the assembled batches comply with the specification limits defined in the International Organization for Standardization (ISO) Standard 11608-1:2012;⁷ and the related requirements for visual inspection. Furthermore, the PDS290 IDegLira pen-injector meets the specifications for total content of device, dose accuracy of last dose, free fall and vibration test.

Quality related proposed conditions of registration

The quality evaluator proposed the following condition of registration:

Batch release testing and compliance with Certified Product Details (CPD)

It is a condition of registration that all batches of Xultophy imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

It is a condition of registration that up to 5 initial batches of Xultophy imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.

The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified product details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Nonclinical

There were no nonclinical objections to the registration of Xultophy for the proposed indications.

- The nonclinical submission was of adequate quality and scope, consistent with relevant TGA-adopted guidelines (ICH M3 (R2);⁸ and

⁷ ISO Standard 11608-1:2012: Needle-based injection systems for medical use. Requirements and test methods Part 1: Needle-based injection systems. International Organization for Standardization.

⁸ International Conference on Harmonisation: ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

EMEA/CHMP/SWP/258498/2005).⁹ The nonclinical dossier contained new studies on primary pharmacology, pharmacokinetics, repeat-dose toxicity and local tolerance performed with insulin degludec and liraglutide in combination. All key safety-related studies were Good Laboratory Practice compliant.

- In a primary pharmacology study in normoglycaemic rats, single subcutaneous (SC) administration of insulin degludec and liraglutide in combination produced dose-dependent reductions in blood glucose, body weight, food consumption and water intake over 24 hours, in line with actions of the individual active components. No further reduction in blood glucose was seen with the combination compared to single-agent insulin degludec; this reflects liraglutide alone having no clear effect in normoglycaemic animals, as this action is glucose-dependent.
- The pharmacokinetics of insulin degludec and liraglutide, alone and in combination, were examined after single SC administration in pigs. The kinetic profile of insulin degludec was not affected by liraglutide co-administration, while lower (peak and overall) exposure was seen for liraglutide when given in combination with insulin degludec, with this attributable to the presence of zinc in the formulation. Decreased maximum (peak) concentration for the liraglutide component (by 23%) with the combination compared with the single-agent was also reported in humans.
- Repeat-dose toxicity studies with insulin degludec and liraglutide in combination were performed by the SC route in rats. The pivotal study was of appropriate duration (3 months) and used the clinical dose ratio and dosing frequency; dose selection was appropriate, limited by hypoglycaemia (primary pharmacological action of insulin degludec), with the highest dose level (20/32 nmol/kg/day insulin degludec/liraglutide) yielding systemic exposure 2- and 3-times higher for the respective active components than in patients at the maximum recommended human dose. No novel or exacerbated toxicity was evident compared with that observed with the individual agents in previously evaluated studies.
- Formulations of insulin degludec/liraglutide resembling the commercial product were shown to be well tolerated locally following injection by the SC route (in rats, rabbits and pigs) and by potential accidental routes (intramuscular and intravenous; in rabbits). Injection site findings were mostly graded minimal to slight in severity, and were not directly related to either active ingredient but rather mostly reflected injection trauma, with a smaller additional contribution by the excipients present.
- Pregnancy Category B3,¹⁰ as the sponsor proposes, is considered appropriate. This matches the existing category for both individual active components.
- Results and conclusions drawn from the nonclinical program for insulin degludec and liraglutide (in combination and as single agents) detailed in the sponsor's draft risk management plan (RMP) are in general concordance with those of the nonclinical evaluator.

⁹ European Medicines Evaluation Agency, Committee for Medicinal Products for Human Use: Non-clinical development of fixed combinations of medicinal products

¹⁰ **Category B3:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Clinical

The clinical component of this submission contained the following:

- Three clinical pharmacology studies: Study NN9068-4026, Study NN9068-3632 and Study NN9068-3871.
- Nine Phase III efficacy and safety studies: Study NN9068-3697, Study NN9068-3851, Study NN9068-3912, Study NN9068-3951, Study NN9068-3952, Study NN9068-4056, Study NN9068-4184, Study NN9068-4185 and Study NN9068-4229
- Summaries of clinical efficacy and clinical safety, and a clinical overview.
- A pharmacovigilance plan and a risk management plan (RMP).

Pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of insulin degludec and liraglutide have been investigated individually and are well characterised.

The PK data in the dossier addressed bioavailability in the fixed dose combination compared to individual administration. These data demonstrated:

- There is equivalent exposure to insulin degludec by combined compared to simultaneous or separate administration.
- There is decreased exposure to liraglutide in combination, by approximately 11% (in terms of area under the concentration-time curve), with a decreased maximum (peak) concentration by 26%.
- Time of maximum (peak) concentration appears to be increased for both actives when administered in combination.

In the opinion of the clinical evaluator, the decreased exposure to liraglutide is not sufficient to be of clinical significance. The increase in time of maximum concentration is unlikely to be of significance in clinical practice.

Pharmacodynamics

Glucose infusion rates were similar for insulin degludec given alongside liraglutide and insulin degludec given in combination with liraglutide. Overall, glucose infusion rate was higher for the treatments containing liraglutide, compared with insulin degludec alone.

Efficacy

The sponsor submitted seven pivotal clinical efficacy and safety studies. Six of these were compared to an alternative active comparator or placebo. One study was to determine if treatment should be titrated once or twice weekly. The results of these studies are summarised in the tables below.

Table 3: Study NN9068-3697

Study NN9068-3697	
Design	Open label, randomised, parallel group, 3 arm treat to target study of insulin degludec + liraglutide versus insulin degludec versus liraglutide alone in patients with T2DM on oral antidiabetic drugs. Non-inferiority study

Study NN9068-3697	
Study treatments	Insulin degludec + liraglutide: 10-50 dose steps Insulin degludec: 10 units and no maximum dose Liraglutide: titrated 0.6 mg Week 1, 1.2 mg Week 2, 1.8 mg Week 3
Patients	834 Insulin degludec + liraglutide 414 Insulin degludec only 415 Liraglutide only Only 1.7% > 75 years, 12.5% > 65 years All patients were on metformin
Results	At 26 weeks, the change in HbA1c; ¹¹ was greater for insulin degludec + liraglutide than insulin degludec (-0.47%) and liraglutide (-0.64%) Similar outcomes were seen at 52 weeks Patients in the insulin degludec + liraglutide group needed a lower dose of insulin More weight loss and less hypoglycaemia in liraglutide alone than in the insulin degludec + liraglutide group

T2DM = type 2 diabetes mellitus; HbA1c = glycated haemoglobin

Table 4: Study NN9068-3851

Study NN9068-3851	
Design	Study NN9068-3851 was an open-label, randomised, two-arm, parallel group, treat-to-target clinical trial of insulin degludec + liraglutide in comparison with unchanged therapy in patients with T2DM, inadequately controlled on GLP-1 receptor agonist therapy in combination with metformin ± pioglitazone ± SU Sample size was based on superiority.
Study treatments	Insulin degludec + liraglutide dose according to a dose titration algorithm. GLP-1 receptor agonist dose unchanged from pre-trial
Patients	292 insulin degludec + liraglutide 146 GLP-1 receptor agonist

¹¹ **Glycated haemoglobin (HbA1c)** is a minor component of haemoglobin chemically linked to glucose. Levels of HbA1c vary and are relative to the overall blood glucose concentration. Unlike a blood glucose concentration, levels of HbA1c are not influenced by daily fluctuations in the blood glucose concentration but reflect the average glucose levels over the prior 6 to 8 weeks. Measurement of HbA1c is used in the diagnosis of diabetes mellitus and is useful indicator of how well the blood glucose level has been controlled in the recent past and can be used to monitor the effects of diabetes management and therapeutic interventions.

Study NN9068-3851	
Results	Difference in HbA1c at Week 26 was 0.94% Body weight increased in the insulin degludec + liraglutide group relative to the GLP-1 receptor agonist group with a difference of 2.89 kg

T2DM = type 2 diabetes mellitus; GLP-1 = glucagon like peptide-1; SU = sulphonylurea; HbA1c = glycated haemoglobin

Table 5: Study NN9068-3912

Study NN9068-3912	
Design	Study NN9068-3912 was a double blind, randomised, parallel group, two-arm treat-to-target clinical trial comparing insulin degludec + liraglutide with insulin degludec alone in patients with T2DM. Superiority study
Study treatments	Insulin degludec + liraglutide according to schedule in PI
Patients	207 insulin degludec + liraglutide 206 insulin degludec
Results	At Baseline, all patients were on metformin. 49.5% were also on SU. There was a greater decrease in HbA1c in the insulin degludec + liraglutide group -1.05% compared to insulin degludec alone Less hypoglycaemia and weight gain in the insulin degludec + liraglutide group

T2DM = type 2 diabetes mellitus; SU = sulphonylurea; HbA1c = glycated haemoglobin

Table 6: Study NN9068-3951

Study NN9068-3951	
Design	Study NN9068-3951 was a double-blind, randomised, parallel group, target to treat study in insulin naïve patients with inadequately controlled T2DM on an oral antidiabetic regimen consisting of SU ± metformin.
Study treatments	Insulin degludec + liraglutide versus placebo
Patients	289 insulin degludec + liraglutide 146 placebo
Results	All patients on SU, 89.6% also on metformin

Study NN9068-3951	
	<p>Insulin degludec + liraglutide was superior to placebo at Week 26: was 1.02 (-1.18 to -0.87) %, p < 0.001</p> <p>Improvement in FPG in insulin degludec + liraglutide group</p> <p>No significant difference in the prandial glucose increments</p>

T2DM = type 2 diabetes mellitus; SU = sulphonylurea; FPG = fasting plasma glucose

Table 7: Study NN9068-3952

Study NN9068-3952	
Design	<p>Study NN9068-3952 was an open-label, randomised, parallel group, two-arm treat-to-target clinical trial of insulin degludec + liraglutide in comparison (non-inferiority study) with insulin glargine.</p> <p>In T2DM</p> <p>Treatment target 4-5 mmol/L</p> <p>Lower insulin dose in insulin degludec + liraglutide group.</p>
Study treatments	<p>Initial starting dose 16 steps insulin degludec + liraglutide</p> <p>On usual insulin glargine dose</p> <p>All patients were on insulin glargine at Baseline (mean dose 31 units) and metformin</p>
Patients	<p>278 randomised to insulin degludec + liraglutide</p> <p>279 to insulin glargine</p>
Results	<p>Insulin degludec + liraglutide was non-inferior to insulin glargine at Week 26: -0.59% (-0.74 to -0.45%), p < 0.001. This was confirmed by a secondary analysis of superiority (p < 0.001, adjusted p value = 0.0250).</p> <p>Less weight gain and less hypoglycaemia in the insulin degludec + liraglutide group</p> <p>Lower insulin dose in insulin degludec + liraglutide group.</p>

T2DM = type 2 diabetes mellitus

Table 8: Study NN9068-4056

Study NN9068-4056	
Design	Study NN9068-4056 was an open-label, randomised, parallel group, two arm clinical trial to compare two different dosing titration regimens for insulin degludec +liraglutide. Non-inferiority study
Study treatments	Both treatment groups received insulin degludec + liraglutide; insulin degludec 100 units/mL and liraglutide 3.6 mg/mL, in 3 mL pre-filled PDS290 pen-injectors. The starting dose was 10 dose steps (10 units insulin degludec and 1.8 mg liraglutide) and the maximum daily dose was 50 dose steps (50 units insulin degludec and 0.36 mg liraglutide). The two alternative titration regimens were: 1. Once weekly titration, based on the mean of 2 fasting SMPG values measured pre-breakfast in the morning of two consecutive days; or 2. Twice weekly titration based on the mean of 3 fasting SMPG values For both regimens the dose adjustment was: Mean SMPG < 4 mmol/L: dose adjusted -2 dose steps Mean SMPG 4.0 to 5.0 mmol/L: no dose adjustment Mean SMPG > 5 mmol/L: dose adjusted +2 dose steps.
Patients	T2DM on metformin +/- pioglitazone (5.2%) 210 weekly titration 210 twice weekly titration
Results	HbA1c decreased at a faster rate in the twice weekly group but there was no significant difference in HbA1c between the treatment groups at Week 32. There was more hypoglycaemia after 8 weeks in the Xultophy group.

T2DM = type 2 diabetes mellitus; SMPG = self-measured plasma glucose; HbA1c = glycated haemoglobin

Table 9: Study NN9068-4184

Study NN9068-4184	
Design	Study NN9068-4184 was a double-blind, randomised, parallel group, two arm, treat-to-target trial comparing insulin degludec + liraglutide to insulin degludec alone in patients with T2DM. Study location: Japan.
Study treatments	Starting dose 10-16 units, maximum dose 50 units for both groups

Study NN9068-4184	
Patients	All patients were on basal insulin with metformin +/- another oral antidiabetic drug. 105 in insulin degludec + liraglutide group, 105 in insulin degludec group
Results	Insulin degludec + liraglutide was superior to insulin degludec: at Week 26 the least square of the mean (SE) for HbA1c was 6.65% (0.08) in the insulin degludec + liraglutide group and 7.93% (0.08) in the insulin degludec; mean (95% CI) difference -1.28% (-1.50 to -1.06), $p < 0.0001$.

T2DM = type 2 diabetes mellitus; SE = standard error; HbA1c = glycated haemoglobin; CI = confidence interval

Table 10: Study NN9068-4185

Study NN9068-4185	
Design	Study NN9068-4185 was an open-label, randomised, parallel group, two arm, treat-to-target trial conducted in patients with T2DM, comparing insulin degludec + liraglutide, with insulin glargine + insulin aspart
Study treatments	Starting dose of insulin degludec + liraglutide was 16 units; maximum of 50 units Starting dose of insulin glargine as per pre-study, starting dose of insulin aspart was 4 units Target range: 4-6mmol/L
Patients	Patients were on metformin and insulin glargine at Baseline 252 insulin degludec + liraglutide 254 insulin glargine + insulin aspart
Results	Non-inferiority was demonstrated for insulin degludec + liraglutide compared to insulin glargine + insulin aspart Much less hypoglycaemia in the insulin degludec + liraglutide group More weight loss in the insulin degludec + liraglutide group Lower insulin dose in the insulin degludec + liraglutide group.

T2DM = type 2 diabetes mellitus

Table 11: Study NN9068-4229

Study NN9068-4229	
Design	Open-label, randomised, parallel group, two-arm treat-to-target trial of insulin degludec + liraglutide compared to insulin glargine, as add-on therapy in patients with T2DM and treated with an SGLT2 inhibitor. This was a non-inferiority study
Study treatments	Insulin degludec + liraglutide: 10-50 units Insulin glargine, starting at 10 units Treat to target: 4-6mmol/L
Patients	All patients were on SGLT-2 inhibitors. 95.5% were also taking metformin
Results	At Week 26 HbA1c had decreased to a greater extent in the insulin degludec + liraglutide group compared to insulin glargine; LS mean (SE) change from Baseline to Week 26 -1.95% (0.05) in the insulin degludec + liraglutide group and -1.61% (0.05) in the insulin glargine; treatment difference (95% CI) insulin degludec + liraglutide group versus insulin glargine, -0.34% (-0.48 to -0.20%), p < 0.0001 (for non-inferiority). No weight loss in insulin degludec + liraglutide group but weight gain in glargine group

T2DM = type 2 diabetes mellitus; HbA1c = glycated haemoglobin; LS = least squares; SE = standard error; CI = confidence intervals.

Safety

The Global Safety Risk Management Plan, dated 25 September 2019, provides data on overall exposure to insulin degludec/liraglutide. There have been 3141 patients exposed to insulin degludec/liraglutide in clinical trials, with 650 patients exposed for \geq 12 months. There were 1706 males and 1435 females. There were 620 patients aged 65 to 74 years, 73 aged 75 to 84 years and 1 aged \geq 85 years.

There were 1305 patients with mild renal impairment, 139 with moderate and 1 with severe. There were 7 patients with hepatic impairment. There were 140 patients with cardiac impairment.

Nausea, vomiting and diarrhoea were commonly reported in the insulin degludec/liraglutide groups.

From 2015, there have been 422 reports of increased lipase from clinical studies and 377 from post market sources. The positive predictive value is 1%.

The rate of hypoglycaemia with insulin degludec/liraglutide varied between the studies. In Study NN9068-4056, there was more hypoglycaemia in the group with twice weekly dose titration.

The rates of neoplasia were not significantly different between insulin degludec/liraglutide and comparators. However, neoplasia is a safety concern for all of the active treatments used in the development program.

Clinical evaluator's recommendation

In the words of the evaluator 'the efficacy data do not provide any support for reduction in *the risk of cardiovascular events in those at high cardiovascular risk*'. All of the studies excluded patients at high cardiovascular risk. Reduction in cardiovascular risk was not an efficacy outcome measure in any of the studies and no hypothesis tests were performed for this outcome measure.

The efficacy data do not provide evidence of efficacy in the absence of background treatment with metformin. There were only 49 patients that were not treated with metformin at Baseline. There was no subgroup, or even post-hoc analysis of efficacy in this patient group. Hence, the efficacy data support the efficacy of insulin degludec/liraglutide in conjunction with background metformin treatment.

There was insufficient detail presented about the dietary and lifestyle advice provided to the patients in the study. Therefore, the data do not provide evidence of efficacy in the absence of dietary and lifestyle advice. Hence, the efficacy data support the efficacy of insulin degludec/liraglutide in conjunction with background dietary and lifestyle interventions.

In response to the evaluator's concerns the sponsor amended the indication to:

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).

Risk management plan

The sponsor has applied to register a new fixed dose combination product, insulin degludec and liraglutide (Xultophy) for subcutaneous injection. Xultophy is proposed to be used for the treatment of adults with T2DM to improve glycaemic control in combination with one or more oral glucose-lowering medicinal products. Xultophy will be available in a single strength pre-filled pen: insulin degludec 100 units/mL, and liraglutide 3.6 mg/mL. The pre-filled pen can provide from 1 up to 50 dose steps in one injection in increments of one dose step. Xultophy is given once daily by subcutaneous administration and is to be dosed in accordance with the individual patient's needs, based on fasting plasma glucose levels.

The sponsor has submitted EU-risk management plan (RMP) version 9.0 (date: 25 September 2019, data lock point (DLP) 31 August 2018) and Australian-specific Annex (ASA) version 0.1 (date 14 November 2018) in support of this application.

At the second round, the sponsor updated the proposed indication to now recommend use of Xultophy as an adjunct to diet and exercise combination with metformin, with or without one or more other oral glucose-lowering medicinal products. The sponsor has submitted an updated an ASA version 0.2 (date 14 July 2020) that includes revisions based on the first round recommendations.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12.¹²

Table 12: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	-	-	-	-
Important potential risks	Medullary thyroid cancer*	Ü	-	Ü	-
	Neoplasms*	Ü	-	-	-
	Pancreatic cancer*	Ü	-	-	-
	Medication errors, including errors with transfer from injectable diabetes therapy*†	Ü	-	Ü	Ü
Missing information	Transfer from basal insulin < 20 units or > 50 units	Ü	-	Ü	-

*Targeted follow up questionnaire; † Healthcare Professional (HCP) education material

The RMP evaluator had the following recommendations at the second round:

Recommendation: The sponsor should address the outstanding recommendations concerning the proposed Healthcare Professional (HCP) brochure to align with the PI recommendation. HCP brochure should include the dosage recommendations when switching from insulin therapies including basal insulin component: '*The recommended starting dose should not be exceeded, but may be reduced to avoid hypoglycaemia in selected cases*'. The sponsor should revise the HCP brochure and provide it to the TGA for approval prior to the supply of Xultophy.

Recommendation: The sponsor should ensure that the outcomes of this distribution effectiveness measure are reported as an appendix to the periodic safety update report (PSUR). In addition, the evaluator brought to the attention of the Delegate the discrepancy in box warning for multidrug therapy between the United States PI and Australian PI. The Delegate accepts the previous decision made in relation to the need for the box warning with liraglutide.

¹² Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

RMP evaluator recommendations regarding conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Xultophy (insulin degludec / liraglutide) EU-Risk Management Plan (RMP) (version 9, dated 25 September 2019, DLP 31 Aug 2018), with Australian Specific Annex (version 0.2, dated 14 July 2020), included with submission PM-2019-05122-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three year period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Risk-benefit analysis

Delegate's considerations

Xultophy is a fixed dose combination of two currently registered products for the treatment of T2DM.

Pending GMP clearance at one of the manufacturing sites, there were no concerns about the quality dossier for Xultophy.

The sponsor has provided an acceptable level of evidence to support use to improve glycaemic control in patients with T2DM with poor glycaemic control despite treatment with metformin +/- other antihyperglycaemic medications. The clinical trials show use in conjunction with a range of medications.

The safety profile is consistent with that of liraglutide and insulin degludec, with less hypoglycaemia and weight gain than patients treated with higher doses of insulin and less gastrointestinal side effects than liraglutide alone.

The Delegate agrees with the clinical evaluator that the indication should be for second line treatment, in patients with poor glycaemic control despite metformin. The Delegate also agrees with the clinical evaluator that there is insufficient evidence to support the use of this fixed dose combination in the prevention of cardiovascular disease.

Conclusion

The Delegate recommends approval of the registration of Xultophy for the sponsor's new proposed indication

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.

Approval is subject to GMP clearance of the remaining manufacturing sites, and the sponsor's response to the recommendations in regards to the PI [discussion of PI recommendations are beyond the scope of the AusPAR].

Advisory Committee considerations¹³

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Xultophy (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL solution) for injection pre-filled pen 3 mL indicated for the following indication:

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).

Specific conditions of registration applying to these goods

- Xultophy (insulin degludec / liraglutide) is to be included in the Black Triangle Scheme.

¹³ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- The PI and CMI for Xultophy must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.
- The Xultophy (insulin degludec / liraglutide) EU-Risk Management Plan (RMP), version 9, dated 25 September 2019 (DLP 31 August 2018), with Australian specific Annex, version 0.2, dated 14 July 2020, included with submission PM-2019-05122-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
- The Consumer Medicines Information must be included with the products as a package insert.
- Batch release testing and compliance with Certified Product Details (CPD)
 - It is a condition of registration that all batches of Xultophy imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
 - It is a condition of registration that up to 5 initial batches of Xultophy imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.
 - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>.
 - This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Attachment 1. Product Information

The PI for Xultophy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at [<https://www.tga.gov.au/product-information-pi>](https://www.tga.gov.au/product-information-pi).

Therapeutic Goods Administration

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