Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Liraglutide

Proprietary Product Name: Victoza, Saxenda

Sponsor: Novo Nordisk Pharmaceuticals Pty. Ltd.

April 2019

TGA Health Safety Regulation

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.

Contents

Common abbreviations

Abbreviation	Meaning
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of covariance
bpm	Beats per minute
BMI	Body mass index
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
CMI	Consumer medicine information
DCCT	Diabetes Control and Complications Trial
eGFR	Estimated glomerular filtration rate
EAC	Event adjudication committee
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
ETD	Estimated treatment difference
FAS	Full analysis set
FDA	Federal Drug Administration
GLP-1	Glucagon-like peptide 1
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
IL6	Interleukin 6
IP	Intraperitoneal (injection)

Abbreviation	Meaning
ITT	Intent to treat
LDL	Low density lipoprotein
MACE	Major adverse cardiovascular event
MDRD	Modified diet for renal disease
NPH	Neutral protamine Hagedorn
NYHA	New York Heart Association
PD	Pharmacodynamic
PI	Product information
PK	Pharmacokinetic
PSUR	Periodic safety update report
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous (injection)
TGA	Therapeutic Goods Administration
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom prospective diabetes study
VLDL	Very low density lipoprotein

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	5 January 2018
Date of entry onto ARTG:	8 January 2018
ARTG numbers:	153980 and 225804
, *Black Triangle Scheme*	No
Active ingredient:	Liraglutide
Product names:	Victoza and Saxenda
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Pty Ltd Level 3, 21 Solent Circuit Baulkham Hills NSW 2153
Dose form:	Solution for injection
Strength:	6 mg/mL
Container:	Prefilled pen 3 mL
Pack sizes:	1, 2, 3, 5 or 10 pens
Approved therapeutic use:	***Victoza*** *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* *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 CLINICAL TRIALS)*. ***Saxenda*** *Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of* • *≥ 30 kg/m² (obese) or* • *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia*

(pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

Route of administration:	Subcutaneous injection
Dosage:	Initial dose 0.6 mg once daily (see PI for details)

Product background

This AusPAR describes the application by the sponsor to register Victoza liraglutide for the following extension of indication:

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*
- *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
- *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*
- *in combination therapy with insulin, with or without metformin.*

Prevention of cardiovascular events:

Victoza is indicated to prevent major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus at high cardiovascular risk, as an adjunct to standard of care therapy (see Clinical Trials).

Liraglutide is also supplied as Saxenda 6 mg/mL prefilled pen which is approved for a different indication to that of Victoza; that is, for long term use in weight control. This submission also contained an application to change details in the Product Information (PI) for Saxenda. The changes proposed; were to include the results of a 3 year follow up of Study 1839; which result in a change to the wording of the indications for Saxenda (specifically the redaction of the reference to long term safety data in the clinical trials section). The proposed indications for Saxenda were:

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of

- *≥ 30 kg/m² (obese)*
- *or≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.*

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

Long term use should be informed by the following:

Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (> 12 months) might not have been identified in the clinical development program (refer Clinical Trials).

Liraglutide is a glucagon-like peptide 1 (GLP-1) agonist, used to lower blood glucose in type 2 diabetes mellitus by stimulating both basal and post prandial glucose dependent insulin release. It is given as a daily subcutaneous injection.

Use of Victoza as monotherapy for glycaemic control was considered as part of the initial application for Victoza (Submission PM-2008-2112-1-5) but was rejected due to lack of data in comparison to metformin, and no data on long term safety.

Cardiovascular disease is the major cause of death in type 2 diabetes mellitus. Diabetes is a major risk factor for cardiovascular disease; however patients with diabetes commonly have other co-morbidities which increase the risk of cardiovascular disease such as obesity, hypertension, and hyperlipidaemia.

Regulatory status

The product Victoza received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 26 August 2010.

At the time of this submission the approved indications for Victoza were:

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

- *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
- *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*
- *in combination therapy with basal insulin, with or without metformin.*

The product Saxenda received initial registration on the ARTG on 24 December 2015.

At the time of this submission the approved indications for Saxenda were:

Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of

- *≥ 30 kg/m² (obese)*
- *or≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.*

Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight. Long term use should be informed by the following:

- *Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (> 12 months) might not have been identified in the clinical development program (refer Clinical Trials).*
- *Long term efficacy data are limited. The treatment effect has only been documented for 1 year (refer Clinical Trials).*

At the time the TGA considered this application; a similar application had been approved in the countries or regions as shown in Table 1.

Table 1: International regulatory status

Country/ Region Trade name	Status Date	Indications
USA Victoza	Approved 25 January 2010	Victoza is a glucagon-like peptide-1 receptor agonist indicated: • as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes • to reduce the risk of major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease.
EU Centralised procedure Victoza	Approved 26 May 2016	Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control as: Monotherapy: • When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications. Combination therapy: • In combination with oral glucose lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.
Switzerland Victoza	Approved 4 July 2017	Glycaemic control Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control as: Monotherapy: • When diet and exercise alone do not provide adequate glycaemic control and metformin is considered unsuitable due to intolerance or contraindication. In combination with: • metformin or a sulphonylurea in patients with inadequate glycaemic control despite the maximum tolerated dose using monotherapy with metformin or a sulphonylurea. In combination with: • metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with inadequate glycaemic control despite therapy with 2 oral antidiabetics. Victoza can be used as a combination therapy with basal insulin and metformin to improve blood glucose control in

Country/ Region Trade name	Status Date	Indications
		adults with type 2 diabetes mellitus.
Canada Victoza	Approved 15 June 2017	Victoza is indicated for once-daily administration for the treatment of adults with type 2 diabetes to improve glycemic control in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • metformin and basal insulin, when diet and exercise plus dual therapy with Victoza and metformin do not achieve adequate glycemic control (see Clinical Trials)
New Zealand	Approved 7 July 2005	Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus

Product Information

The Product Information (PI) documents approved with the submission which is described in this AusPAR can be found as Attachment 1 (Victoza) and Attachment 2 (Saxenda). For the most recent PI documents, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

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-2016-03931-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	1 February 2017
First round evaluation completed	6 July 2017
Sponsor provides responses on questions raised in first round evaluation	6 September 2017
Second round evaluation completed	13 October 2017

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 October 2017
Sponsor's pre-Advisory Committee response	10 November 2017
Advisory Committee meeting	30 November and 1 December 2017
Registration decision (Outcome)	approved
Completion of administrative activities and registration on ARTG	8 January 2018
Number of working days from submission dossier acceptance to registration decision*	193

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

Introduction

The proposed extension of indication for Victoza includes for the prevention of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus. The sponsor submitted two primary pharmacology studies in support of the new cardiovascular indication, as well as a number of published papers.

Pharmacology

Primary pharmacology

The effect of liraglutide treatment was examined in two well-established animal models of atherosclerosis; apolipoprotein E (ApoE) gene knockout mice and low density lipoprotein (LDL) receptor knockout mice, both fed a Western (high fat, high cholesterol) diet to accelerate plaque lesion development.[1],[2]

Treatment with liraglutide (1 mg/kg/day subcutaneous (SC) injection) significantly reduced aortic plaque lesion development in both models:

- ApoE knockout mice showed a 26% decrease in plaque area with treatment for 15 weeks; and

[1] Getz G.S. and Reardon C.A. (2012) Animal models of atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 2012; 32:1104–1115
[2] Zadelaar S., et al. (2007) Mouse models for atherosclerosis and pharmaceutical modifiers. *Arterioscler. Thromb. Vasc. Biol.* 2007; 27:1706–1721

- LDL receptor knockout mice showed a 78% decrease in plaque area with treatment for 17 weeks, with no plaque lesions found in around half of the treated animals.

Liraglutide treatment also reduced body weight, and had beneficial effects on plasma lipids, decreasing plasma triglyceride, total cholesterol, LDL cholesterol and very low density lipoprotein (VLDL) cholesterol, and increasing high density lipoprotein (HDL) cholesterol. The study in ApoE knockout mice additionally showed attenuation of aortic intima thickening by liraglutide, that the effect of liraglutide to reduce aortic plaque area was not due to the concomitant reduction in body weight, and that liraglutide did not cause regression of an established plaque.

Treatment with liraglutide was also associated with changes in expression of multiple genes in the aorta, in particular down regulation of genes involved in inflammatory pathways (such as leukocyte recruitment, adhesion and migration) and representing markers for extracellular matrix protein turnover. This included the genes for osteopontin (SPP1) and interleukin 6 (IL-6), which are recognised to have a positive association with cardiovascular disease.[3,4]

The two studies offer support for the proposed extension of indication to include prevention of cardiovascular events. Further support comes from published literature that showed:

- from genomic screening, that a missense variant in the gene encoding the GLP-1 receptor that was associated with lower fasting glucose (as seen with activation of the receptor by liraglutide) was also associated with protection against heart disease in humans;[5]
- that native GLP-1 and other GLP-1 receptor agonists (for example, exenatide) reduce inflammation in multiple sites, including the heart and blood vessels, in various mouse models;[6]
- that liraglutide; as well as inhibiting progression of atherosclerotic plaque formation; also significantly enhanced plaque stability in ApoE knockout mice (with treatment at 0.3 mg/kg twice daily SC; assessed by measurement of vascular smooth muscle cell α-actin content, lipid deposition, collagen content and macrophage staining within plaques in cross-sections of the brachiocephalic artery;[7]
- that treatment with liraglutide (0.2 mg/kg twice daily intraperitoneal (IP) injection) for 7 days prior to induction of myocardial infarction significantly increased survival and cardiac output, and reduced cardiac rupture and infarct size, in wild-type mice,[8] with cardio-protection shown to be independent of GLP-1 receptor signalling in subsequent experiments with genetically modified mice with cardiomyocyte-specific inactivation of the GLPR1 gene;[9] and

[3] Looker H.C. et al. (2015) Protein biomarkers for the prediction of cardiovascular disease in type 2 diabetes. *Diabetologia.* 2015; 58:1363–1371
[4] IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N. et al. (2012) Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet.* 2012; 379: 1205–1213
[5] Scott R.A. et al. (2016) A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. *Sci. Transl. Med.* 8:341ra76
[6] Drucker D.J. (2016) The Cardiovascular Biology of Glucagon-like Peptide-1. *Cell Metab.* 2016; 24:15–30
[7] Gaspari T. et al. (2013) The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE$^{-/-}$ mouse model. *Diab. Vasc. Dis. Res.* 2013; 10:353–360
[8] Noyan-Ashraf M.H. et al. (2009) GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes.* 2009; 58:975–983
[9] Ussher J.R. et al. (2014) Inactivation of the cardiomyocyte glucagon-like peptide-1 receptor (GLP-1R) unmasks cardiomyocyte-independent GLP-1R-mediated cardioprotection. *Mol. Metab.* 2014; 3:507–517.

- that thrombus formation was greater in mice transplanted with bone marrow from GLP-1 receptor knockout mice compare with mice that received wild-type bone marrow, suggesting attenuation of platelet function and prevention of thrombus formation by GLP-1R agonists as potential mechanisms for reduced atherothrombotic events.[10]

Nonclinical summary and conclusions

Newly submitted pharmacology studies and published literature offer support for the efficacy of liraglutide in the prevention of major adverse cardiovascular events.

There are no nonclinical objections to the proposed extension of indications for Victoza.

V. Clinical findings

Introduction

This is a submission to make a total of eight changes to the statements of indication and product information (PI) for the sponsor's liraglutide products Victoza and Saxenda. The submission also included changes to the currently approved PI which are not part of this AusPAR. In the letter of application the sponsor has numbered these V1 to V4 and S1 respectively, referring to the following:

- V1: extension of indication to include restricted monotherapy, and in addition an update to the dosage recommendation to state that no dose adjustment is required for patients with hepatic impairment. Note that as stated in the letter of application 'this change is grouped within the monotherapy indication updates as a result of the EU submission history where both changes were requested together.'
- V2: extension of indications to include unrestricted monotherapy, that is, approval for use as sole therapy unconstrained by the type 2 diabetes mellitus patient's suitability for or responsiveness to other therapy, particularly metformin.

The sponsor is not requesting two new monotherapy indications, but essentially two alternatives for approval. V1 has been approved in the EU, and V2 submitted there.

- V3: extension of indications to include prevention of cardiovascular events, as noted by the final paragraph of the proposed new indication shown below, but also broadening the indication for use of the product with insulin by removal of the word basal so that use with any form of insulin therapy will be permitted; and by an alteration to the PI relaxing a contraindication and some precautions based on long term safety data in a significant number of patients with various sensitivities (for example, heart failure, pancreatitis, renal impairment). Note that justification of all of these changes is based on the findings of Study 3748 (the LEADER trial).
- V4: inclusion in the Victoza PI of the results of a comparator trial of liraglutide versus lixisenatide as add-on to metformin in subjects with type 2 diabetes mellitus (Study 3867).
- S1: long term weight management and in consequence, deleting statements in the Indications and Dosage and Administration sections which refer to efficacy of the treatment only having been documented for 1 year.

[10] Cameron-Vendrig A. et al. (2016) Glucagon-Like Peptide 1 Receptor Activation Attenuates Platelet Aggregation and Thrombosis. *Diabetes.* 2016; 65:1714–1723

The current statement of indications for Victoza is:

> *Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:*
>
> - *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
> - *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*
> - *in combination therapy with basal insulin, with or without metformin*.

Changes V1 and V2 relating to use as monotherapy are supported in this submission *inter alia* by a pivotal study, Study 1573, and three Phase II studies: Studies 1571, 1310 and 2072. All four of these studies have been previously evaluated for TGA and those evaluations are reviewed in the relevant sections of this report. Pharmacokinetic Studies 1328 and 1329, included in the tabular listing of studies for this submission, were also evaluated in an earlier submission.

Clinical rationale

Liraglutide in type 2 diabetes mellitus

As a GLP-1 agonist, liraglutide exerts its anti-hyperglycaemic action by stimulating insulin release from beta cells in a glucose-dependent fashion, while at the same time inhibiting glucagon release, likewise in a glucose-dependent fashion. Its effective action in patients with diabetes mellitus is therefore dependent on at least some degree of residual beta cell function and is appropriate for the treatment of type 2 but not type 1, diabetes. It is effective for the control of both fasting and post-prandial hyperglycaemia. These actions are fully documented in the existing approved PI which summarises the data upon which its original registration for the treatment of type 2 diabetes mellitus was based.

Stimulation of prandial insulin secretion by secretagogues including GLP-1, the so-called incretin effect, is recognised as an important component of the physiology of insulin secretion, and has been shown to be deficient as part of the pathophysiology of type 2 diabetes mellitus. The use of incretin based therapies for treatment of type 2 diabetes mellitus, including GLP-1 analogues such as liraglutide, is therefore scientifically rational, including their use as monotherapy.

Liraglutide in weight management

Liraglutide lowers body weight through decreased food intake and loss of predominantly fat mass. Liraglutide affects the four main components of appetite. Liraglutide regulates appetite by increasing feelings of fullness and satiety, while lowering feelings of hunger and prospective food consumption. It is effective for weight management as an adjunct to diet and exercise. These actions are documented in the existing approved PI which summarises the data upon which its original registration for the treatment of obesity and overweight was based.

Obesity and overweight are usually long term or chronic conditions, and the proposed long term use of liraglutide in weight management is also scientifically rational.

Guidance

There is a declaration of compliance with the pre-submission planning form and letter applicable to both the Victoza and Saxenda products, but no other record of any guidance received from TGA. The sponsor has however been provided with considerable guidance

by the European Medicines Agency (EMA) in the course of its application in the EU, as outlined in the following section.

Contents of the clinical dossier

The dossier is well presented and the comprehensive covering letter very useful in navigating the rather complex submission.

The submission contained the following clinical information:

- 4 pivotal efficacy/safety studies, one of which had been previously evaluated and was referred to but data not included.
- 3 other efficacy/safety studies, previously evaluated and referred to but data not included.

Paediatric data

The submission did not include paediatric data.

Good Clinical Practice

The submission provides assurance that both the previously and newly evaluated studies in the submission were conducted in accordance with the Declaration of Helsinki and the International Conference for Harmonisation (ICH) Guideline on Good Clinical Practice (GCP).

Pharmacokinetics

No pharmacokinetic data were submitted with this application. The pharmacokinetic properties of liraglutide applicable to both the Victoza and Saxenda products are well characterised and accurately summarised in the approved PI for both.

Pharmacodynamics

No pharmacodynamic data were submitted with this application. The mechanism of action of liraglutide as a GLP-1 agonist is well understood and its pharmacodynamics properties are accurately summarised in the existing PI for both Victoza and Saxenda.

Dosage selection for the pivotal studies

In both pivotal Studies 1573 and 3748 supporting the monotherapy indication for Victoza, the dosage schedule for liraglutide was the same as that advised in the current PI and used in clinical practice, 0.6 mg increasing by 0.6 mg increments at weekly intervals to a daily maintenance dose of 1.8 mg or less according to tolerance. 1.8 mg daily is the maximum recommended therapeutic dose and is the same dose as was used in the pivotal efficacy study for a previous submission to TGA.

Efficacy

Studies

The following studies were considered by the clinical evaluator for the following aspects of this submission:

- V1 and V2; restricted and unrestricted monotherapy in type 2 diabetes mellitus:
  - Study 1573
- V2 and V3; unrestricted monotherapy and cardio-protection:
  - Study 3748 (the LEADER trial)
  - Other efficacy studies: Studies 1571, 1310 and 2072
- V4: liraglutide versus lixisenatide as add-on to metformin:
  - Study 3867
- Saxenda in obesity management:
  - Study 1839; 3 year results.

Evaluator's conclusions on efficacy

Conclusions regarding efficacy as monotherapy (changes V1 and V2)

Efficacy of liraglutide as monotherapy in type 2 diabetes mellitus is clearly shown by Study 1573. No conclusion can be drawn regarding the relative efficacy of liraglutide respective to metformin in terms of treatment size effect, that is, glycosylated haemoglobin (HbA1c) reduction, at least at the proposed liraglutide dosage of 1.8 mg. A possible interpretation of Study 2072, which showed liraglutide to be equivalent to metformin at a dosage, which in the light of subsequent evidence, is probably subtherapeutic, is that liraglutide might be more effective than metformin at the proposed 1.8 mg dose, but the sponsor appropriately makes no speculation in that respect.

Conclusions regarding efficacy in prevention of cardiovascular events (change V3)

Study 3748 (LEADER trial) demonstrates efficacy in this respect, with a risk reduction for major adverse cardiovascular event (MACE) of 13% which is clinically as well as statistically significant. Given that diabetes control was also significantly improved in the actively treated group, no conclusion can be drawn regarding the risk reduction being a specific effect of liraglutide as opposed to being a consequence of the improved glycaemic control.

Conclusions regarding efficacy in obesity management (change S1)

This conclusion depends on what is regarded as the objective of managing obesity. If it is to reduce the incidence of type 2 diabetes mellitus in obese subjects at risk of developing diabetes, then long term (3 year) administration of liraglutide is certainly effective, at least for as long as the drug is continued (Study 1839). If on the other hand the criterion is continuing weight loss with long term administration of liraglutide, then it is not effective.

Safety

Studies providing safety data

The following studies included in the submission provided evaluable safety data: Study 3748, Study 3867, and Study 1839. These are all classified as pivotal to the various aspects of the submission and their safety data are described below both collectively and as they impact those aspects. The safety data for the remaining pivotal Study 1573 has been evaluated previously.

Note that this submission does not contain an integrated summary of clinical safety. Separate summaries of safety are presented as addenda to each of the three study reports.

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were documented and reported to the sponsor by the investigators in the usual way, employing standard clinical record and adverse event reporting forms.
- AEs of particular interest were collected, particular those relating to issues specified as being of special interest.
- Laboratory tests, including full haematological assessment, standard clinical chemistry profile, lipid profile, urinalysis and assessment of renal function, were performed at regular intervals as specified in the study protocols. In addition, special laboratory tests of interest include regular measurements of plasma calcitonin, amylase and lipase.

Patient exposure

1.8 mg liraglutide dosage

In Study 3748, some 9340 subjects were exposed to trial product, 4668 to liraglutide and 4672 to placebo. Median duration of exposure for the liraglutide group was 3.52 years and for placebo, 3.51 years. Total exposure to liraglutide expressed as patient-years of exposure, was 14,502 patient-years and to placebo 14,157 patient-years.

In Study 3867, a total of 404 subjects were exposed to trial products. The total exposure was 94.19 patient-years for liraglutide, and 92.15 patient-years for lixisenatide.

3 mg liraglutide dosage

In Study 1839, a total of 2248 subjects were exposed to trial products. The total exposure, reflecting the 2:1 randomisation schedule, was 3161 patient-years for liraglutide and 1442 patient-years for placebo. Mean and median duration of exposure for liraglutide was 2.1 and 3.1 years respectively, and for placebo 1.9 and 2.2 years respectively.

Safety issues with the potential for major regulatory impact

Pancreatitis

In Study 3748, the rates of events of pancreatitis were comparable between the liraglutide group (18 events, 0.4% of population) and placebo (23, 0.5%) and the severity of these events were also similar.

No events of pancreatitis were identified in Study 3867. Given the population size (202 per group), the low incidence described in Study 3748, and the much shorter duration of Study 3867, this is not surprising.

By contrast, in Study 1839, 12 subjects had Event Adjudication Committee-confirmed pancreatitis in the entire trial period. Of the adjudicated events, 10 events with liraglutide and 2 events with placebo were confirmed as pancreatitis and the proportions of subjects with Event Adjudicating Committee confirmed pancreatitis events and the rates of events were higher with liraglutide (0.67% of subjects, 0.29 events per 100 patient-years of observation) than with placebo (0.27% of subjects, 0.13 events per 100 patient-years of observation). Most (8 of the 10) events in the liraglutide group occurred during the first year of treatment, whereas in the placebo group they occurred at approximately 40 weeks and 130 weeks respectively.

The cluster of events of pancreatitis in the first year of Study 1839 appears to be a real finding and the contrast with the other studies is striking. A plausible explanation would be that this is related to the higher dosage of liraglutide (3.0 mg) used in Study 1839.

Heart rate

In Study 3748, a small but statistically significant increase in heart rate was observed in the liraglutide group by comparison with placebo at 3 years (estimated treatment difference 2.980 beats per minute (bpm) ($p < 0.001$). A similar mean increase of 2.50 bpm was found in the liraglutide subjects of Study 3867 but did not occur in the lixisenatide group for which a mean decrease of -1.10 bpm was observed. A mean increase in heart rate of 2 bpm was also observed in Study 1839, which also reported a higher rate of episodes classified as 'syncope and tachycardia' in the liraglutide group (0.6 events per 100 patient-years of observation, by comparison with 0.4 in the placebo group). None of these was classified as serious, and the overall incidence of cardiac arrhythmias was similar in the two groups.

Other events of special interest

In Study 3748, acute gallstone disease occurred more frequently in the liraglutide group, but not markedly so (145 events, 3.1%), than with placebo (90 events, 1.9%). In the other large study reviewed, 1839, this difference was numerically more marked: the proportions of subjects with 'acute gallstone disease' AEs and the rates of events were higher with liraglutide (4.9%, 2.9 events per 100 patient-years of observation) than with placebo (1.7%, 1.2 events per 100 patient-years of observation).

As for pancreatitis, the association of a higher rate of adverse event with the 3.0 mg dose of liraglutide is noted.

Event rates for both benign and malignant neoplasms were very similar in the two treatment groups of Study 3748, with no statistically significant treatment difference being observed. A similar pattern was found in Study 3867 and likewise in Study 1839 in which a total of 276 neoplasm AEs were identified (including benign, premalignant, malignant, unspecified neoplasms as well as polyps and cysts) in 179 subjects with liraglutide 3.0 mg by comparison with 139 events in 86 subjects with placebo.

In Study 1839, three of the events were classified as 'thyroid neoplasms', all in the liraglutide group. The narratives for these show that they were all papillary micro-carcinomas, that is, not calcitonin related and were all incidentally found on histopathology following thyroidectomy for other reasons. This is a not uncommon finding following thyroidectomy and is not felt to be treatment-related. In any case the 3:0 distribution is not surprising given the 2:1 randomisation in this study.

Deaths and other serious adverse events

In Study 3748, as already noted, cardiovascular death occurred in a lesser proportion of liraglutide than placebo subjects whereas non cardiovascular deaths occurred in a similar proportion in the liraglutide group (162, 3.5%) as in the placebo group (169, 3.6%). No unusual pattern of distribution of deaths or serious adverse events (SAEs) otherwise occurred between the two groups.

In Study 3867, no deaths were reported. SAE were reported more frequently for liraglutide subjects (138 events per 1000 patient-years) than with lixisenatide (76 events per 1000 patient-years).

During the 172 weeks of Study 1839, there were only 4 deaths; the study report records the remarkable finding that '4 subjects had 5 events with fatal outcomes', but in fact there were 2 deaths in each study group, neither appearing likely to be treatment related.

The disparity between the overall death rates in the studies is attributable to the age of the study populations and their comorbidities. Mean age of the high cardiovascular risk Study 3748 population was 64.3 years whereas that of the Study 1839 population was 47.5 years.

Discontinuation due to adverse events

In Study 3748, permanent withdrawal of treatment due to a serious adverse event occurred in similar proportions of the liraglutide group (4.2%) by comparison with the placebo group (5.3%). This was also the case by comparison with lixisenatide in Study 3867.

In Study 1839, apart from the withdrawals due to pancreatitis (7 liraglutide, 1 placebo) 191 liraglutide subjects and 43 placebo subjects withdrew due to adverse events. The majority of these AE were gastrointestinal disorders, accounting completely for the imbalance between the active and placebo groups: 118 liraglutide treated subjects (7.9%) withdrew for this reason by comparison with 11 (1.5%) placebo subjects.

Laboratory tests

Liver function

No significant differences were detected between active and comparator or groups in any of the reviewed studies. Some minor changes in liver enzymes found in Study 1839 but were mostly transient and none appeared of clinical significance.

Kidney function

In Study 3748, the decrease in the estimated glomerular filtration rate (eGFR) at 3 years was significantly smaller in the liraglutide group, by a margin of 1 to 2%, than in the placebo group. No significant changes in renal function were identified in Study 3867.

In Study 1839, acute renal failure was specified as an AE of interest. This was identified in 20 liraglutide and 11 placebo subjects, the proportion of expectation with the 2:1 randomisation ratio.

Other clinical chemistry

In Study 3748, the proportion of subjects with post-baseline levels of calcitonin above 20 ng/L was similar in both liraglutide and placebo groups (3.1% and 3.0% respectively). Similar findings were reported in Study 3867. In Study 1839, some elevations of plasma calcitonin were noted: the proportion of subjects with elevated calcitonin AEs and event rates were low in both treatment groups although higher with liraglutide (1.3%, 0.8 events per 100 patient-years of observation) than with placebo (0.7%, 0.5 events per 100 patient-years of observation).

In Study 3748, amylase levels increased by approximately 14% in the liraglutide group and 6% in the placebo group whereas lipase levels increased by 33% in the liraglutide group and 4% in the placebo group. Likewise in Study 3867, the changes in these enzymes were more marked for liraglutide subjects than with lixisenatide. A similar pattern was seen in Study 1839, in which mean serum lipase rose by approximately 30%, although remaining within the reference range, within the first 4 weeks and remained stable at the elevated level for the duration of the study, then returning towards normal during the off-drug period. Amylase levels did not change significantly.

Haematology

No significant differences were detected over time between active and comparator or groups in any of the reviewed studies.

Post-marketing data

The sponsor's pharmacovigilance policy has been provided, including availability of periodic safety update report (PSURs) but no data of this type was included. This is not considered important for the purpose of this report, as both products involved are already registered and the target populations are unchanged.

Evaluator's conclusions on safety

The safety profile of liraglutide was comprehensively evaluated for the original registration of the product. That evaluation included consideration of a number of the studies supporting the current submission, including pivotal Study 1573 submitted in support of the monotherapy indication. It is therefore considered appropriate to reproduce below the safety summary from that review and to comment further upon it on the basis of the additional data in the current submission. The summary is as follows:

> *Liraglutide has been in clinical use in Australia for 5 years, at a dose of 1.8 mg as compared to the 3 mg requested in this application and PSUR data to date has not revealed any new signals. However this is a drug that binds almost 24 hours to stimulate a receptor and because obesity is a chronic problem may be taken long term. Therefore long term pharmacovigilance data is paramount.*
>
> *Apart from gastrointestinal events which were reported in an increasing amount to the 1.8 mg dose (up to 50% had nausea in one study); overall a dose response relationship was not able to be ascertained for other safety events.*
>
> *The clinical significance of a pulse rate increase of 2 to 3 bpm was not discussed however there are agents registered in Australia to lower heart rate based on translational evidence showing that higher heart rates are associated with higher death rates. Results of multiple ongoing cardiovascular outcome trials (including LEADER with liraglutide in type 2 diabetes mellitus) will help clarify the long term cardiovascular risk of liraglutide. The cardiovascular trial data is awaited from studies currently underway and observation for thyroid disease, hepato-biliary disease, thyroid cancers and hypoglycaemia continues.*
>
> *There were a number of adverse events seen in the liraglutide 3 mg group in this application that occurred at a higher rate than the placebo group. These include pancreatitis and gallbladder disease. Amylase and lipase concentrations were consistently elevated across the trials in the liraglutide 3 mg arm; this resolved on drug cessation supporting the drug-event relationship.*
>
> *The risk of hypoglycaemia was reported in the liraglutide group even in the non-type 2 diabetes mellitus group. A total of 8 severe treatment emergent hypoglycaemic episodes were reported, 5 events by 3 subjects (0.7%) with liraglutide 3mg, and 3 events were reported by 2 subjects (1.0%) with liraglutide 1.8 mg; all subjects were taking sulphonylureas as background diabetes medication.*
>
> *Safety was not examined in groups excluded from partaking in the study but who may be eligible to take the drug if marketed, depending in the listing. 93% of the exposure was in subjects in the age group 18 to 65 years. Similarly, few subjects with renal impairment were included in the trials.*
>
> *10 of the 39 pregnancies that occurred in the trials resulted in spontaneous abortion (8 with liraglutide 3 mg and 2 with placebo).*

The current safety evaluation supports all of the above observations and extends them as follows:

- With regard to the important question of dose dependency of adverse effects, this evaluation had the opportunity to compare the incidence and severity of AEs in two large studies employing the recommended liraglutide dosage for Victoza (1.8 mg, Study 3748) and that for Saxenda (3.0 mg, Study 1839). It is clear that adverse effects are more common at the higher dose level; nausea and other gastrointestinal disorders have a higher incidence, with almost twice as many subjects withdrawing for such reasons in Study 1839; pancreatitis occurs at a low but more clearly defined level with a placebo adjusted risk of approximately 0.3% in the first year of administration;

and acute gallstone disease occurred at a higher rate, more clearly different from that in the placebo group as was the case in the 1.8 mg daily study.

- The basal heart rate increase of 2 to 3 bpm is confirmed by all of the included studies but appears not to be associated with any cardiovascular risk, as Study 3748 (LEADER trial) showed liraglutide to be of benefit regarding cardiovascular risk when used in type 2 diabetes mellitus.
- Hypoglycaemia was again seen but appears to be a minor issue accompanying improved glycaemic control and in the setting of associated use of other antidiabetic therapies including insulin.
- No new evidence emerged in these studies of increasing or persistent elevation of calcitonin secretion or clinical sequelae thereof, for example, medullary thyroid carcinoma, although again there was a suggestion of more calcitonin stimulation at the 3 mg dose level, with more levels above the reference range during drug administration.

No previously unidentified risks or new types of adverse event were evident in this evaluation. The longer term studies have shown no further increase in the level of any neoplasia risk, although this remains a matter of concern: note that the 3 new cases of breast cancer identified in the long term phase of Study 1839 brings the total of such cases to 17 (0.76%) of 2379 Saxenda treated women compared with 3 (0.2%) of 1300 women treated with placebo. The observation of the previous evaluator regarding ongoing pharmacovigilance being paramount is supported.

First round benefit-risk assessment

Separate benefit-risk assessments are provided below for each of the indication changes proposed in the submission.

Some of these benefit-risk assessments, and the consequent recommendations, are influenced by the complex relationship between diabetes (both type 1 and type 2), glycaemic control of diabetes, and the risk or incidence of vascular disease. It is considered beyond the scope of this report to include a comprehensive and referenced review of this subject, but the evaluator believes few would disagree with the following:

- It is well established that both types of diabetes are associated with an increased risk of both micro and macro vascular disease.
- The landmark Diabetes Control and Complications Trial (DCCT) published two decades ago established that intervention with strict glycaemic control reduced the incidence of microvascular disease (specifically retinopathy) in type I diabetes. The subsequent United Kingdom Prospective Diabetes Study (UKPDS) showed that complications of type 2 diabetes mellitus, including vascular disease, could be reduced by improving glycaemic and/or blood pressure control.
- The question of whether such benefits of glycaemic control in type 2 diabetes mellitus might be specific to one or other form of blood glucose lowering therapy has been more difficult to establish. There has been evidence, some disputed, that particular agents (for example, sulphonylureas orglitazones) might not have such a beneficial effect or even an adverse one and this has led to regulatory authorities requesting cardiovascular outcome studies as part of the approval process for antidiabetic therapies. It is important to recognise that the focus of such requests is to demonstrate a lack of harm for any particular agent; the overall beneficial effect of blood glucose lowering therapy should not be regarded as being in dispute.

V1: restricted monotherapy

First round assessment of benefits

It should be noted that this is not the sponsor's preferred option; unrestricted monotherapy is applied for (Change V2). Furthermore '*restricted monotherapy'* is not clearly defined in the application. It would usually mean monotherapy when metformin is either contraindicated or not tolerated; metformin being generally accepted as first-line therapy; but could additionally be taken to mean '*monotherapy if metformin is ineffective'*. The benefits of Victoza in the proposed usage are:

- Improved glycaemic control as has been shown in the monotherapy setting by the included studies.
- Reduction in cardiovascular risk (Study 3748) and other generally accepted benefits of better glycaemic control including improved well-being.

First round assessment of risks

The risks of Victoza in the proposed usage are:

- Necessity for an injectable as opposed to oral therapy.
- High chance of some of the well demonstrated adverse effects of liraglutide, particularly nausea and other gastrointestinal complaints which although unpleasant are unlikely to have severe health consequences.
- Low but definite possibility of other documented adverse effects such as to gallbladder disease and pancreatitis.
- Uncertainty regarding possible long term and as yet unknown adverse effects.

First round assessment of benefit-risk balance

The benefit-risk balance of Victoza, given the proposed usage, is favourable taking into account the proviso that use of metformin is excluded.

V2: unrestricted monotherapy

First round assessment of benefits

The benefits of Victoza in the proposed usage are essentially the same as those stated for change V1, as follows:

- Improved glycaemic control as has been shown in the monotherapy setting by the included studies.
- Reduction in cardiovascular risk (Study 3748) and other generally accepted benefits of better glycaemic control including improved well-being.

First round assessment of risks

The risks of Victoza in the proposed usage, likewise, are:

- Necessity for an injectable as opposed to oral therapy.
- High chance of some of the well demonstrated adverse effects of liraglutide, particularly nausea and other gastrointestinal complaints which although unpleasant are unlikely to have severe health consequences.
- Low but definite possibility of other documented adverse effects such as to gallbladder disease and pancreatitis.
- Uncertainty regarding possible long term and as yet unknown adverse effects.

First round assessment of benefit-risk balance

The benefit-risk balance of Victoza, given the proposed usage, is favourable although not as favourable as metformin would be in the same setting assuming that the latter was well tolerated and effective.

V3: use to prevent cardiovascular events; use with any insulin rather than only basal insulin; relaxing of contraindications regarding a history of heart failure, pancreatitis or renal impairment

First round assessment of benefits

The benefits of Victoza in the proposed usage are as for the other changes, but in particular:

- Reduction in risk of major cardiovascular events for type 2 diabetes mellitus patients with high cardiovascular risk.
- Potential benefit for a wider range of patients on existing insulin regimens or with a history of the stated conditions.

First round assessment of risks

The risks of Victoza in the proposed usage are as for the other changes, but in addition:

- Possible increased risk of hypoglycaemia for patients on more complex insulin regimens.
- The possibility that the risk of using Victoza in patients with the stated comorbidities has been underestimated by the studies done so far.

First round assessment of benefit-risk balance

The benefit-risk balance of Victoza, given the proposed usage, is favourable. The risk of hypoglycaemia is tolerable in the context that glycaemic control is at the same time being improved. Any persisting risk in use with the stated comorbidities can be adequately managed with continuing pharmacovigilance.

S1: long term obesity management

First round assessment of benefits

The benefits of Saxenda in the proposed usage which, in terms of the requested change, is taken to mean usage beyond 12 months and up to 3 years, are:

- To significantly reduce the risk of development of type 2 diabetes mellitus, as long as the drug is continued.

First round assessment of risks

The risks of Saxenda in the proposed usage are:

- For the majority of patients treated, a failure to achieve the stated objective of the treatment which is continuing weight loss.
- Exposure to an increased risk of adverse effects at the 3 mg liraglutide dose level by comparison with the 1.8 mg level.

First round assessment of benefit-risk balance

The benefit-risk balance of the proposed PI change for Saxenda is unfavourable. The reason for this conclusion is that the statement of indication states that the drug is to be used as an adjunct to weight management; hence, statements regarding the treatment

effect are likely to be and should be interpreted as referring to changes in weight. Study 1839 clearly showed that the overall mean result was for no further weight to be lost after 12 months.

First round recommendation regarding authorisation

V1: restricted monotherapy

Restricted monotherapy, which is taken to mean monotherapy for type 2 diabetes mellitus patients in whom metformin is either contraindicated or not tolerated, should be approved.

A statement of indication so worded acknowledges the place of metformin as preferred first-line therapy for type 2 diabetes mellitus patients who do not respond to lifestyle measures alone, which has long been the recommendation of the joint position statement of American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD).[11] That document is widely regarded as the leading evidence-based guideline on the use of blood glucose lowering therapies, and continues to recommend metformin as first-line therapy in its latest version. In its more recent iterations, including the present one, it also acknowledges that the choice of second-line agent (that is, once metformin has been excluded either because it is contraindicated, not tolerated, or ineffective) has become more complex and can be interpreted as taking the view that such choice may be left to the treating doctor in the light of supporting evidence and the patient's particular clinical circumstances. This philosophy would support the availability of liraglutide (Victoza) as second-line therapy for patients in whom metformin cannot be used. For patients in whom metformin is simply ineffective, the prescriber already has the option of adding Victoza under the currently approved indications.

V2: unrestricted monotherapy

Full monotherapy, which would permit use without a trial of metformin, is not recommended by this evaluator for the following reasons:

- No evidence has been produced of liraglutide being more effective than metformin in a treatment-naive type 2 diabetes mellitus patient presenting for initial pharmacotherapy.
- The risk-benefit analysis provided above does not support such use.
- The ADA and EADS guideline referred to above does not recommend the use of liraglutide (or any other agent) in preference to metformin as first-line therapy.

V3: cardio-protection

Prevention of cardiovascular events, as it appears in the proposed new statement of indication, is not an ‘extension of indication’, as stated in the letter of application, but a completely new indication parallel to and separate from that of ‘glycaemic control’ in the existing statement. The wording of the statement isolates this new indication from the primary indication of use in liraglutide which is to improve glycaemic control in type 2 diabetes mellitus. It reads more like a statement of indication for a cholesterol-lowering or blood pressure reducing drug in type 2 diabetes mellitus.

[11] Inzucchi SE, et al Management of hyperglycaemia in type II diabetes, 2015: a patient-centred approach. Updated position statement of the American diabetes Association and European Association for the study of diabetes. *Diabetologia* 2015; 58:429-442

The sponsor is to be commended for organising Study 3748 (the LEADER trial), whose findings have been much anticipated. However it is stretching interpretation of these findings to introduce prevention of cardiovascular events as a separate indication independent of glycaemic control; reference is made to the introductory statement at the beginning of this section. Study 3748 showed that the subjects experienced an improvement in glycaemic control and a reduction in cardiovascular events. It did not produce any evidence that the second finding was anything other than a consequence of the first, or propose a mechanism where such might be the case as a result of some unique property of liraglutide as distinct from other blood glucose lowering agents.

Separating the two indications has the potential to create situations in which patients might be exposed to risks of unnecessary therapy. A particular and common example would be a patient with type 2 diabetes mellitus who comes under excellent control by the usual criteria as a result of lifestyle measures, with or without the addition of metformin. Should this patient have other risk factors denoting high cardiovascular risk (for example, dyslipidaemia, hypertension), standard of care therapy would demand these be appropriately managed. This new indication would then suggest that the patient should in addition be given liraglutide (Victoza). The risk-benefit analysis as conducted by this evaluation would not support that therapeutic decision, which would in any case be against existing guidelines such as the ADA/EASD statement already referred to.

It would be more appropriate for the two indications to be linked, along the lines:

> '*Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, and to prevent major cardiovascular events when there is associated high vascular risk, as:*
>
> - *monotherapy,….. et cetera'*

Accordingly it is recommended that the sponsor consider a revised statement of indication of this nature.

Broadening the indication from combination therapy with basal (only) insulin to include any type of insulin is acceptable on the basis of the evidence and it is recommended that this be approved; additionally, on the grounds of simplicity for the prescriber.

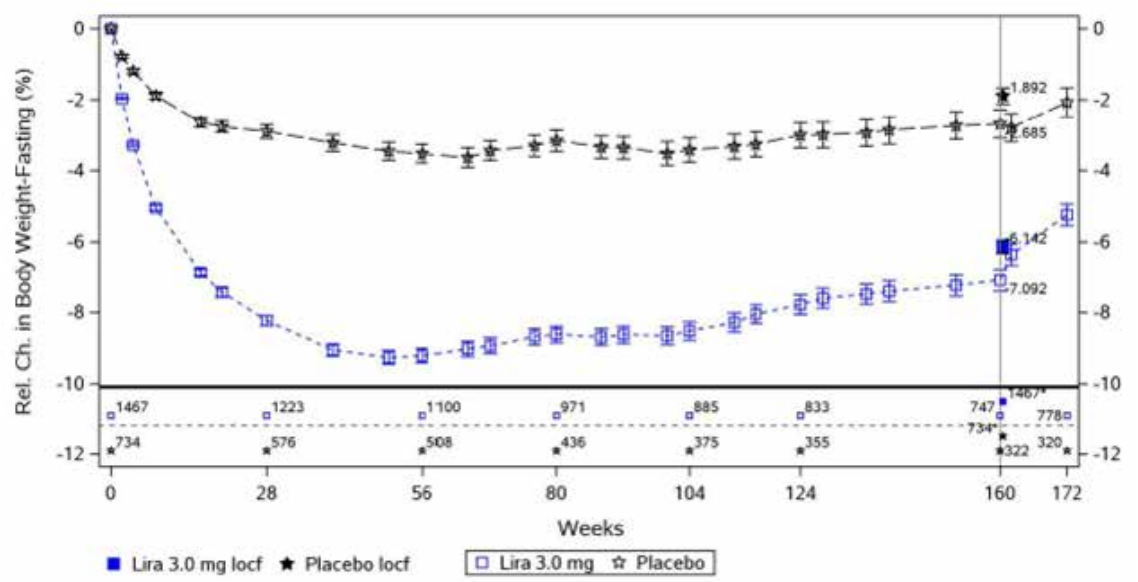
Relaxing the contraindication and precautions statements in regard to the stated sensitivities (heart failure, pancreatitis, and renal impairment) is also acceptable and should be approved.

Note: the sponsor is not suggesting that pancreatitis be removed as a potential adverse effect of liraglutide, just that a previous history of pancreatitis is not a confounding or additional risk. Also note that in the draft Saxenda PI, there remains a statement that it is not recommended for use in patients with a history of pancreatitis as such patients were excluded from the clinical trials.

S1: long term obesity management

It is not recommended that the requested changes be approved as presently stated. The background to this is explained in the relevant benefit-risk assessment. Removal of the cautionary note regarding the absence of long term efficacy data implies that long term efficacy is now established. With regard to weight reduction, this is not the case, as outlined above and illustrated by Figure 1. The statement in the letter of application that the 160 week part of Study 1839 *'……..confirmed the long term efficacy of Saxenda in weight management*' is disputed. Long term assessment of weight reduction was not even stated as an objective of the study; the sponsor's own description of the study in the draft Saxenda PI confirms this. What the study did show in these obese subjects was a significant and worthwhile reduction in the rate of progression to type 2 diabetes mellitus.

Figure 1: Relative change (%) in fasting bodyweight from Baseline over time (0 to 172 weeks); Full analysis set (FAS)

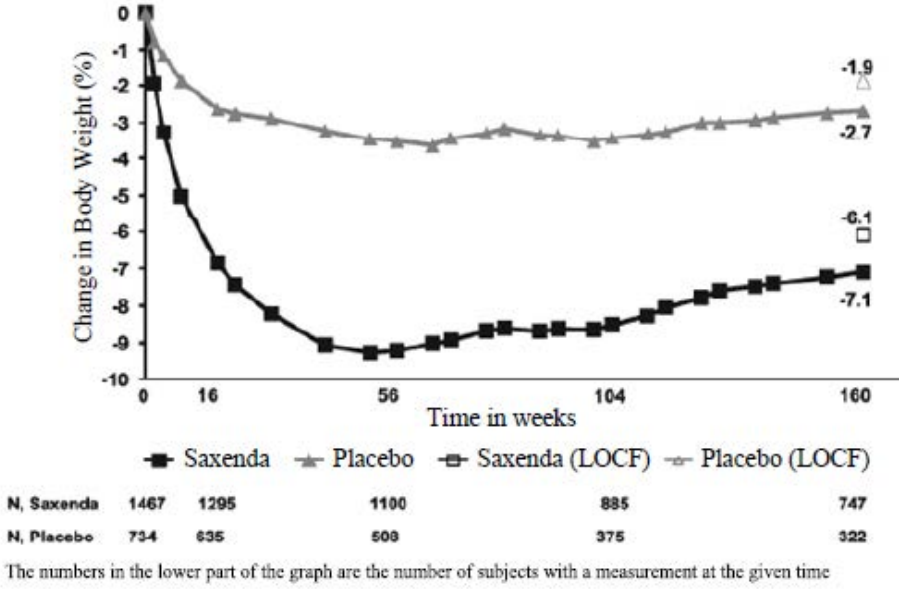


One of the criteria for approval of weight reducing drugs is the relevant EU guideline which stipulates a placebo adjusted weight loss of > 5%. At the time of its original TGA registration on the basis of the one year data, Saxenda achieved that criterion with a figure of 5.4%; at 160 weeks, but the placebo adjusted weight loss had fallen to 4.3%.

There are two statements proposed for deletion. One is in the Indications section and reads '*long term efficacy data are limited. The treatment effect has only been documented for one year*'; the other is in the Dosage and Administration section and reads '*the treatment effect has only been documented for one year. The need for continued treatment should be re-evaluated whenever a new prescription is written or at least annually*'.

The failure for weight loss to progress beyond the first year is clearly illustrated in the draft PI in Figure 2 and by comparison of Tables 3 and 4 although there is no comment in the text to this effect except that earlier, in the section on body weight, the following statement appears: '*the weight loss occurred mainly in the first year, and was sustained throughout the 160 weeks*'. It would be more consistent with the data if this simply said 'the weight loss occurred mainly in the first year'.

Figure 2: Change from Baseline in bodyweight (%) by time in SCALE-Obesity and pre-diabetes (0 to 160 weeks)



SCALE = Satiety and clinical adiposity liraglutide evidence; LOCF = last observation carried forward

Table 3: SCALE-Obesity and pre-diabetes; changes from Baseline in bodyweight, glycaemia and cardiometabolic parameters at Week 56

	Saxenda® (N=2437)		Placebo (N=1225)		Saxenda® vs. placebo
Body weight					
Baseline, kg (SD)	106.3 (21.2)		106.3 (21.7)		-
Mean change at week 56, % (95% CI)	-8.0		-2.6		-5.4** (-5.8; -5.0)
Mean change at week 56, kg (95% CI)	-8.4		-2.8		-5.6** (-6.0; -5.1)
Proportion of patients losing ≥5% body weight at week 56, % (95% CI)	63.5		26.6		4.8** (4.1; 5.6)
Proportion of patients losing >10% body weight at week 56, % (95% CI)	32.8		10.1		4.3** (3.5; 5.3)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA1c, %	5.6	-0.3	5.6	-0.1	-0.23** (-0.25; -0.21)
FPG, mmol/L	5.3	-0.4	5.3	-0.01	-0.38** (-0.42; -0.35)
Systolic blood pressure, mmHg	123.0	-4.3	123.3	-1.5	-2.8** (-3.6; -2.1)
Diastolic blood pressure, mmHg	78.7	-2.7	78.9	-1.8	-0.9* (-1.4; -0.4)
Waist circumference, cm	115.0	-8.2	114.5	-4.0	-4.2** (-4.7; -3.7)
Lipids					
Total cholesterol, mmol/L	5.0	-3.2%	5.0	-0.9%	-2.3** (-3.3; -1.3)
LDL cholesterol, mmol/L	2.9	-3.1%	2.9	-0.7%	-2.4* (-4.0; -0.9)
HDL cholesterol, mmol/L	1.3	2.3%	1.3	0.5%	1.9* (0.7; 3.0)
Triglycerides, mmol/L	1.4	-13.6%	1.5	-4.8%	-9.3** (-11.5; -7.0)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 56 are estimated means (least-squares) and treatment contrasts at week 56 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. For lipids, baseline values are geometric means, changes from baseline at week 56 are relative changes, and treatment contrasts at week 56 are relative treatment differences. Missing post-baseline values were imputed using the last observation carried forward. * $p<0.05$.** $p<0.0001$ CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

SCALE = Satiety and clinical adiposity liraglutide evidence

Table 4: SCALE-Obesity and pre-diabetes; changes from Baseline in body weight, glycaemia and cardiometabolic parameters at Week 160

	Saxenda® (N=1472)		Placebo (N=738)		Saxenda® vs. placebo
Body weight					
Baseline, kg (SD)	107.6 (21.6)		108.0 (21.8)		
Mean change at week 160, % (95% CI)	-6.2		-1.8		-4.3** (-4.9; -3.7)
Mean change at week 160, kg (95% CI)	-6.5		-2.0		-4.6** (-5.3; -3.9)
Proportion of patients losing ≥5% body weight at week 160, % (95% CI)	49.6		23.4		3.2** (2.6; 3.9)
Proportion of patients losing >10% body weight at week 160, % (95% CI)	24.4		9.5		3.1** (2.3; 4.1)
Glycaemia and cardiometabolic factors	Baseline	Change	Baseline	Change	
HbA1c, %	5.8	-0.4	5.7	-0.1	-0.21** (-0.24; -0.18)
FPG, mmol/L	5.5	-0.4	5.5	0.04	-0.4** (-0.5; -0.4)
Systolic blood pressure, mmHg	124.8	-3.2	125.0	-0.4	-2.8** (-3.8; -1.8)
Diastolic blood pressure, mmHg	79.4	-2.4	79.8	-1.7	-0.6 (-1.3; 0.1)
Waist circumference, cm	116.6	-6.9	116.7	-3.4	-3.5** (-4.2; -2.8)
Lipids					
Total cholesterol, mmol/L	5.0	-2.9%	5.1	-1.2%	-1.8* (-3.3; -0.2)
LDL cholesterol, mmol/L	2.9	-4.6%	3.0	-2.6%	-2.0 (-4.3; 0.4)
HDL cholesterol, mmol/L	1.3	4.9%	1.3	3.9%	1.0 (-0.6; 2.7)
Triglycerides, mmol/L	1.5	-11.7%	1.5	-5.91	0.94** (0.91; 0.97)

Full Analysis Set. For body weight, HbA_{1c}, FPG, blood pressure and waist circumference, baseline values are means, changes from baseline at week 160 are estimated means (least-squares) and treatment contrasts at week 160 are estimated treatment differences. For the proportions of patients losing ≥5/>10% body weight, estimated odds ratios are presented. For lipids, baseline values are geometric means, changes from baseline at week 160 are relative changes, and treatment contrasts at week 160 are relative treatment differences. Missing post-baseline values were imputed using the last observation carried forward.
* p<0.05.** p<0.0001 CI=confidence interval. FPG=fasting plasma glucose. SD=standard deviation.

SCALE = Satiety and clinical adiposity liraglutide evidence

This is not to say, of course, that continuing weight loss will not occur in some patients. The facts of the situation might be better served by retaining a cautionary statement along the following lines:

'Long term data show that while there is effective prevention of progression to type 2 diabetes, weight loss does not continue in the majority of patients beyond the first year of

treatment with Saxenda. The need for continued treatment should be re-evaluated whenever a new prescription is written, or at least annually'.

This would best be placed at the end of the *Indications* section, in place of the statement proposed for deletion. The statement about the need for continued treatment being periodically re-evaluated is still in place in the draft PI, and should remain.

It is recommended that a change of this nature be reviewed with the sponsor.

Clinical questions

There are no questions beyond those which are implied in the recommendations made regarding non-approval or changes to the draft PI.

Second round evaluation

In this section, comments are made in response to two documents dated 17 August 2017 provided to TGA by the sponsor. The statements and questions raised in these documents are addressed separately as follows.

Recommendation against approval of unrestricted monotherapy for Victoza

In their response, the sponsor continues to argue for approval of this indication which would permit use of liraglutide in preference to metformin as first-line therapy. The sponsor reiterates and expands upon the evidence supporting efficacious use of liraglutide as monotherapy, including in treatment-naive type 2 diabetes mellitus patients and including the data from the LEADER trial included in the submission. None of this is disputed. The sponsor acknowledges that there is no head-to-head study of the efficacy of liraglutide by comparison with metformin as monotherapy for type 2 diabetes mellitus. Even if such did exist and show greater efficacy for liraglutide in the setting of a group study, it remains likely that the study population would consist of metformin responders and non-responders.

An important new document cited in the sponsor's response is the treatment guideline and associated algorithm contained in the consensus statement of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE).[12] This guideline document was published in February 2017 at the time the first-round report was being prepared. The response document cites the guideline as recommending agents including liraglutide as monotherapy and includes the statement in its request for approval of the drug as first-line monotherapy. This is not precisely what the AACE/ACE consensus statement recommends: it prefers metformin as initial therapy and importantly recommends that metformin is continued, if ineffective as initial monotherapy, in combination with the next agent to be introduced (for example, liraglutide). What the guideline/algorithm does do, consistent with the recommendation of other expert bodies as previously discussed, is give greater precedence than previously to GLP-1 agonists (for example, liraglutide) as a therapeutic choice. All of this is entirely consistent with the recommendations in the first round report and it continues to be the evaluator's recommendation that this indication for restricted monotherapy is the one which should be approved.

[12] Garber AJ et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. *Endocrine Practice* 2017; 23: 207-238

Recommendation 2 (Victoza: cardiovascular indication)

Reference is made to the first-round recommendation in which the evaluator points out that the section of the sponsor's proposed statement of indication referring to cardiovascular protection is essentially a new indication rather than an extension of indication and suggested a modification in which the property of cardiovascular protection was incorporated into their glycaemic control indication. In its response, the sponsor has agreed that their application is indeed seeking approval for a new separate indication and continues to argue for this, reiterating the robust findings of the LEADER trial in relation to the reduced incidence of MACE; which the evaluator does not dispute; but (the sponsor) arguing quite directly that this cardiovascular protective effect is *'independent from the well-characterised glucose lowering effect of liraglutide'*. In support of this the sponsor has provided a detailed analysis from the LEADER trial and other clinical trials of the effects of liraglutide on such other cardiovascular risk factors as plasma lipid fractions and inflammatory markets. The sponsor also cites nonclinical (animal) data supporting a direct effect of liraglutide on the atherosclerotic process. The clinical evaluator has not reviewed this preclinical data and cannot pass expert comment upon it. In their conclusion regarding this matter, the sponsor postulates that *'the nonclinical mechanistic data provide the most plausible mechanism for the effect on MACE.'*

The essential question therefore is whether the beneficial effect of liraglutide on cardiovascular outcomes is a consequence of its efficacious effect on glycaemic control or a separate effect independent of glycaemia. If it is the former, liraglutide is doing a good job of being an effective antidiabetic therapy; if the latter, the sponsor's proposed statement of indication suggests that liraglutide be added to the therapeutic regimen of any adult with type 2 diabetes mellitus at high cardiovascular risk (which could readily be interpreted as all of them), as adjunctive treatment additional to their standard diabetes care; which might be as simple as lifestyle measures, with or without metformin. To reiterate, this section of the proposed statement of indication reads as follows:

> *Victoza is indicated to prevent major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus at high cardiovascular risk, as an adjunct to standard of care therapy (see Clinical Trials).*

This would place liraglutide in the same place in the overall treatment algorithm for type 2 diabetes mellitus as is currently occupied by, for example, low-dose aspirin or the use of a statin agent; both of which are commonly used as cardio-protective agents in this context. Apart from the fact that the data so far relates entirely to exposure of patients with type 2 diabetes mellitus, it is possible that this suggested 'independent of diabetes' effect of liraglutide might lead to a proposal for is used in the population at large with high cardiovascular risk for other reasons.

An obvious possibility is that liraglutide improves cardiovascular risk by more than one or possibly multiple mechanisms of action. Just as the sponsor has suggested the 'plausible mechanistic direct effect', the evaluator in the first-round report suggests that the most plausible mechanism might be via the anti-hyperglycaemic effect. There is support for both hypotheses, but some uncertainty as to their relative contribution. In view of this the evaluator continues to prefer the single combined statement of indication as suggested in the first-round report as follows:

> *'Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, and to prevent major cardiovascular events when there is associated high vascular risk, as:*
>
> - *monotherapy,….. et cetera.'*

The evaluator recognised that this is an opinion based on balance of probabilities rather than a robust scientific conclusion. It also takes account of the fact that these statements of indication become recommendations to the prescriber regarding the treatment of individual patients and for that reason should at least in my view be influenced by a degree of responsible therapeutic caution.

The evaluator also notes that in several places the sponsor quotes, as a precedent, the similar indication recently granted for empagliflozin (Jardiance). The evaluator expects, without any special knowledge of the matter, that the arguments for and against the granting of the indication were similar to those posed in the above paragraphs.

Recommendation 4 (Saxenda: long term weight loss)

The sponsor disagrees with the evaluator's recommendation that the proposed PI changes not be approved and instead that a cautionary statement be included in the PI along the lines:

> '*Long term data show that while there is effective prevention of progression to type 2 diabetes, weight loss does not continue in the majority of patients beyond the first year of treatment with Saxenda. The need for continued treatment should be re-evaluated whenever a new prescription is written, or at least annually*'.

The evaluator has given careful consideration to the arguments presented by the sponsor in their response and in the first place do concur with the sponsor's assertion that a plateau of weight loss, as was evident beyond the first year of treatment with Saxenda in Study 1839, inevitably occurs with any form of treatment. Accordingly, at the very least the evaluator agreed that if a statement of the above nature was to be adopted, it should include after the word Saxenda the phrase 'but is maintained at the achieved level'.

Whatever is decided, the evaluator also agrees that the word 'chronic' should continue to be included in the statement of indication in relation to 'weight management' wherever that is mentioned.

With regard to their quotation of the requirements of the 2016 EMA guideline which also reflects the views of the American College of Cardiologists and American Heart Association, the results of Study 1839 do meet; although at the minimal effective level, the criteria for a degree of weight loss which is likely to have discernible metabolic effects. Nevertheless the evaluator thinks prescribers should be aware that long term management with Saxenda is, in the spectrum of available treatments for weight reduction, at the lower end of effectiveness as measured by the amount of weight loss. 4 to 5% is in the order of what is achieved by community self-help programs as opposed to the figures achieved with measures such as protein sparing modified fasting or bariatric surgery, which are up to an order of magnitude greater.

The sponsor also argues on the basis of 'consistency with overseas labelling' that their original request to remove all cautionary statements be agreed to, so that there would be no advice in the PI regarding such a basic matter as the need for continuing treatment to be re-evaluated whenever a new prescription is written or at least annually. The fact that such a statement exists in the current Australian PI but not in those approved by other jurisdictions should not necessarily be regarded as a deficiency in our system rather than theirs.

Second round benefit-risk assessment

No changes from first round benefit-risk assessment.

VI. Pharmacovigilance findings

Risk management plan (RMP)

Summary of RMP evaluation[13]

- The sponsor is seeking approval to extend the indications and update the Product Information (PI) document for Victoza. The sponsor is also seeking approval to update the PI for Saxenda.
- In addition to the above, the sponsor requests an exemption from the TGA requirement to enclose the PI as a package insert for both Victoza and Saxenda.
- To support the application for Victoza, the sponsor has submitted EU-RMP version 27.0 (date 20 October 2016; data lock point (DLP) 30 June 2016) and Australian specific annexe (ASA) version 2.1 (date 7 November 2016). No EU RMP or ASA has been submitted for Saxenda with the current application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies for Victoza are summarised below in Table 5.

Table 5: Summary of safety concerns and associated pharmacovigilance and risk minimisation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypoglycaemia in combination with other anti-glycaemic agents	ü	–	ü	–
	Gastrointestinal AEs	ü	–	ü	–
	Hyperglycaemia due to discontinuation of insulin	ü	–	ü	–
	Altered renal function	ü	–	ü	–
	Allergic reaction	ü	–	ü	–
	Acute gallstone disease	ü	–	ü	–
Important potential risks	Medullary thyroid cancer (C-cell carcinogenicity)	ü	ü*	ü	–
Missing information	Children and adolescents < 18 years	ü	ü#	ü	–

[13] *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.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Pregnant and lactating women	ü	–	ü	–
	Patients with severe hepatic impairment	ü	–	ü	–
	Patients with end-stage renal disease	ü	–	ü	–
	Congestive heart failure NYHA IV	ü	–	ü	–
	Off-label use, including abuse due to weight-lowering potential	ü	–	ü	–
	Drug–drug interaction with warfarin	ü	–	ü	–

#Clinical trial *Patient registry; NYHA= New York heart association

- All safety concerns are addressed with routine pharmacovigilance measures. Additional pharmacovigilance measures are being carried out for medullary thyroid cancer and use in children and adolescent < 18 years.
- Only routine risk minimisation activities are proposed for all safety concerns.

Recommendations

There are no critical recommendations for these submissions.

- It is requested to use bookmarks in the ASA during its next revision to allow for easy navigation through the document.

A second round RMP review was not required.

Risk minimisation plan

If this application results in any changes to the content of the additional risk minimisation materials for Saxenda, the sponsor should submit updated versions of these materials to the TGA.

Advice to the delegate

The sponsor is seeking as exemption from the TGA's condition of registration for injectable products to include the PI as a package insert and proposes to include the Consumer Medicine Information (CMI) in the pack. The RMP evaluator considers that the CMI contains clear instructions on how to use this self-administered injection and illustrations to explain the safe use of the product.

VII. Overall conclusion and risk/benefit assessment

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

Background

Liraglutide is a GLP-1 agonist, used to lower blood glucose in type 2 diabetes mellitus by stimulating both basal and post prandial glucose dependent insulin release. It is given as a daily subcutaneous injection.

Liraglutide was first registered in Australia in 2010.

Monotherapy

Use of Victoza as monotherapy was considered as part of the initial application for Victoza (submission PM-2008-2113-1-5) and rejected due to lack of data in comparison to metformin, and no data on long term safety. The evidence for use as monotherapy comes from a pivotal Study 1573; the three Phase II Studies 1571, 1310 and 2072; and additional studies demonstrating long term safety (the LEADER trial) and use in hepatic and renal impairment.

Currently, New Zealand and the FDA has an unrestricted indication, the EU has a restricted monotherapy indication.

Cardiovascular disease prevention

Cardiovascular disease is the major cause of death in type 2 diabetes mellitus. Diabetes is a major risk factor for cardiovascular disease; however patients with diabetes commonly have other co-morbidities which increase the risk of CV disease such as obesity, hypertension, and hyperlipidaemia.

The EU acknowledged the benefits of liraglutide for CV prevention, however were concerned that some of the findings in the subgroup analysis of exploratory endpoints were conflicting, and that there was an increase in risk of retinopathy. There was also uncertainty about the mechanism of CV protection.

The wording of the indication for Victoza in the EU is:

> *Victoza is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise*
>
> - *as monotherapy when metformin is considered inappropriate due to intolerance or contraindications*
> - *and in addition to other medicinal products for the treatment of diabetes.*
>
> *For study results with respect to combinations, effects on glycaemic control and CV events see sections 4.4, 4.5 and 5.1.*

The FDA approved the indication:

> *VICTOZA is a glucagon-like peptide-1 receptor agonist indicated:*
>
> - *as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes*
> - *to reduce the risk of major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease.*

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The sponsor submitted two papers examining the pharmacodynamic effect of liraglutide in two well established animal models of atherosclerosis. These included in ApoE knockout mice and LDL receptor knockout mice, both fed a high fat high cholesterol diet to accelerate plaque development. Treatment with 1 mg/kg/day of liraglutide resulted in a 26% reduction in plaque area after 15 weeks in the ApoE knockout mice, and a 78% decrease in plaque area after treatment for 17 weeks in the low density lipoprotein receptor knock out mice.

The non clinical evaluator had no non clinical objections to the extension of indication for cardiovascular risk.

Clinical

Efficacy

Monotherapy for liraglutide for glycaemic control

The pivotal Study 1573 was performed over 10 years ago. It compared liraglutide 1.2 mg and 1.8 mg to glimepiride 8 mg daily in 746 subjects with type 2 diabetes mellitus. Superiority for reducing HbA1c and weight loss was demonstrated for liraglutide compared to glimepiride. There was also an improvement in insulin resistance, plasma glucagon, free fatty acids and systolic blood pressure.

Table 6: Analysis of covariance (ANCOVA) of primary endpoint; change in HbA1c (%), ITT populations

Treatment / Comparison	Estimates		P-value
Least Square Means	N	Mean SE	
Lira1.8mg	234	-1.136 0.081	
Lira1.2mg	236	-0.843 0.080	
Glimepiride	241	-0.513 0.077	
Estimated Treatment Differences	LSMean	95% CI	
Lira1.8mg - Glimepiride	-0.623	[-0.826 ; -0.421]	<.0001
Lira1.2mg - Glimepiride	-0.329	[-0.531 ; -0.127]	0.0014
Lira1.8mg - Lira1.2mg	-0.294	[-0.497 ; -0.091]	0.0046

The estimates are from ANCOVA model with treatment, country and previous OAD treatment as fixed effects and baseline value as a covariate.

A Phase II Study 2072 compared liraglutide doses up to 0.75 mg to 1000 mg metformin twice daily. There was no statistical difference in the HbA1c or fasting plasma glucose between the three highest liraglutide groups and metformin after 12 weeks of treatment (it would have been interesting to compare higher doses of metformin).

Liraglutide is not excreted or metabolised by the liver or kidney. In patients with renal or hepatic impairment, there is a decrease in area under the plasma/time curve. Studies in mild to moderate renal and hepatic impairment have shown no difference in efficacy or safety.

The evaluator concluded: 'the benefit-risk balance of Victoza as restricted monotherapy is favourable. The benefit-risk balance of Victoza as an unrestricted monotherapy option, is less favourable as metformin is efficacious and more safe and a better initial monotherapy option'.

Cardiovascular protections

Study 3748, the LEADER trial

Description: This was a very large, long-term, multicentre, international, randomised, double blind, parallel group, placebo controlled trial to determine liraglutide effects on cardiovascular events. The study involved the recruitment over 12,000 subjects and was conducted at 410 sites in 32 countries distributed over major regions of the world including Europe, North and South America, Asia, the Middle East, South Africa, and Australia.

Objectives

The primary objective was to assess the effect of treatment with liraglutide compared to placebo for at least 3.5 years and up to 5 years on the incidence of cardiovascular events, as defined by the primary and secondary endpoints, in adults with type 2 diabetes mellitus that are at high risk for cardiovascular events.

Secondary objectives were to assess efficacy and safety with regard to clinically important events or other surrogate parameters of treatment with liraglutide compared to placebo in adults with type 2 diabetes mellitus that are at high risk for cardiovascular events.

Inclusion criteria

Male or female subjects with type 2 diabetes mellitus with a HbA1c ≥ 7.0% ; antidiabetic drug naïve or treated with one or more oral antidiabetic drugs or treated with human neutral protamine Hagedorn (NPH) insulin or long-acting insulin analogue or premixed insulin, alone or in combination with other anti-diabetic drugs aged:

- ≥ 50 years with at least one of the following criteria: prior myocardial infarction; prior stroke or prior transient ischemic attack; prior coronary, carotid or peripheral arterial revascularisation; > 50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries; history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes, asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo; chronic heart failure NYHA class II or III; chronic renal failure, having clinically reached a stage corresponding to a glomerular filtration rate < 60 mL/min/1.73m^2 per modification of diet in renal disease (MDRD) or < 60 mL/min per Cockroft-Gault formula; or
- ≥ 60 years with at least one of the following criteria: micro albuminuria or proteinuria; hypertension and left ventricular hypertrophy by ECG or imaging; left ventricular systolic or diastolic dysfunction by imaging; ankle/brachial index < 0.9.

Intervention

Liraglutide up to 1.8 mg or placebo + standard care (Standard care involved physicians being able to optimise glycaemic control and other cardiovascular risk factors by other medications).

Outcomes

- The primary endpoint was the time from randomisation to first occurrence of a composite cardiovascular endpoint (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.
- Other outcomes: HbA1c, bodyweight, blood pressure, lipids, expanded MACE, microvascular endpoints.

Statistics

This was designed as a non inferiority trial to fulfil regulatory requirements to prove cardiovascular safety. The required sample size was estimated based on time to first

MACE. Calculations using the full analysis set showed that a total of 611 events provided 90% power to reject the null hypothesis that the upper limit of the two-sided 95% confidence interval (CI) for the hazard ratio was ≥ 1.3.

Baseline criteria

In the full analysis set, mean age was 64.3 years and body weight 91.7 kg (BMI 32.5); 35.7% were female. Mean duration of diabetes prior to the study was 12.8 years and mean baseline HbA1c was 8.7%. The majority of subjects (77.5%) were white.

Most (96.1%) of the subjects were on some form of antidiabetic medication at baseline. 51.5% were on oral agents only, 36.7% on a combination of insulin and oral therapy and 7.9% on insulin alone. 76.5% subjects were taking metformin and 50.7% a sulphonylurea either individually or in combination.

Results

MACE: The hazard ratio (95% CI) for liraglutide versus placebo was 0.87 (0.78 to 0.97) confirming non-inferiority ($p < 0.001$) but also superiority of liraglutide ($p < 0.005$), corresponding to a 13% risk reduction for liraglutide compared to placebo. A favourable effect is observed in all three cardiovascular endpoints.

The composite expanded MACE endpoint consisted of the six following Event Adjudication Committee confirmed cardiovascular events: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure, hospitalisation for unstable angina pectoris and coronary revascularisation.

The hazard ratio for expanded MACE was 0.88 (0.81 to 0.96) 95% CI.

The liraglutide group also experienced a statistically better improvement in HbA1c (estimated treatment difference (ETD) -0.4%), body weight (ETD -2.2kg), systolic BP (ETD -1.2 mmHg). In subjects who were insulin naïve at baseline, the likelihood of initiating insulin was reduced by 48% in the liraglutide group compared to the placebo group.

Overall, the AE profile was consistent with previous studies. There was a reduction in microvascular endpoints related to nephropathy, but a numerically greater number of patients with retinopathy. The increased risk of retinopathy has not previously been seen in nonclinical studies or previous studies with liraglutide. There was no increased risk of pancreatitis or neoplasms.

Figure 3: Kaplan-Meier plot of time to first event adjudication committee (EAC) confirmed MACE; FAS

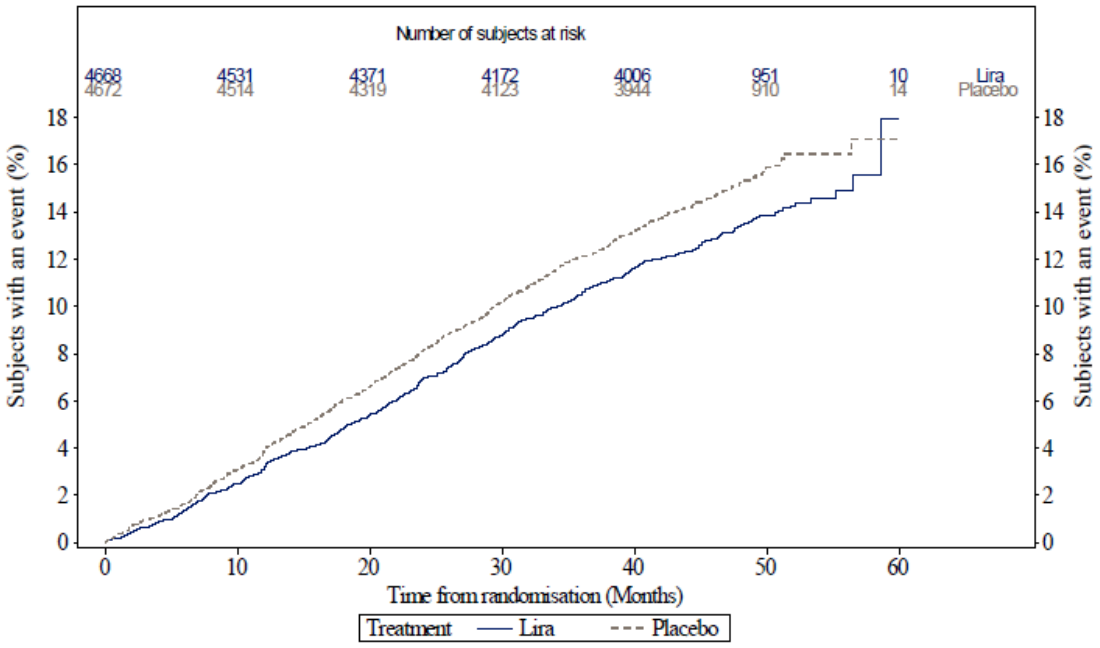
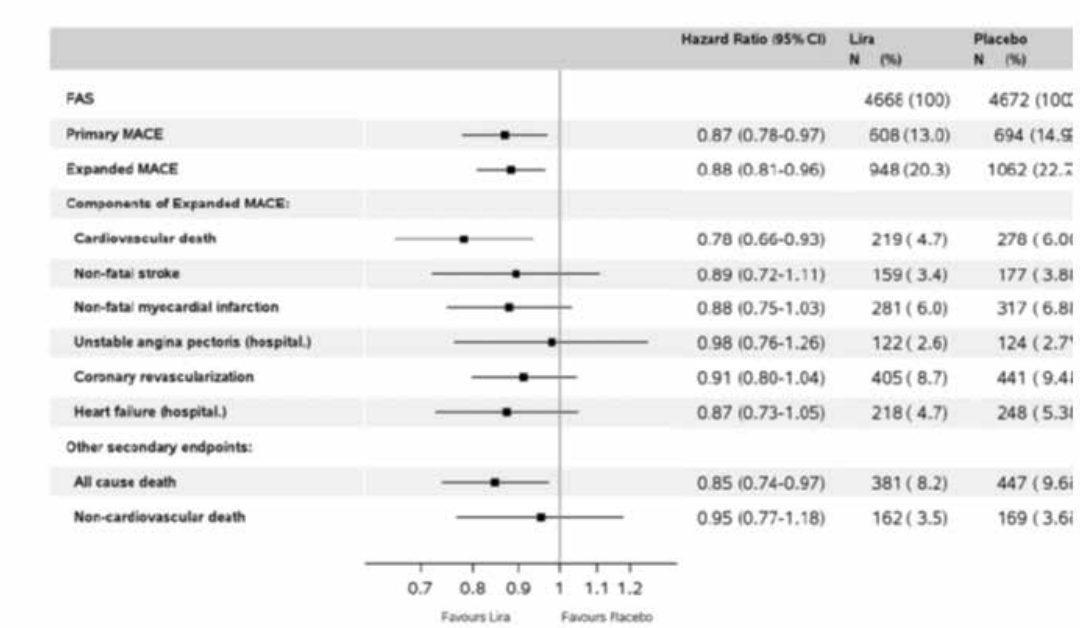


Figure 4: Forest plot of treatment contrast for components of first EAC confirmed expanded MACE, MACE and death

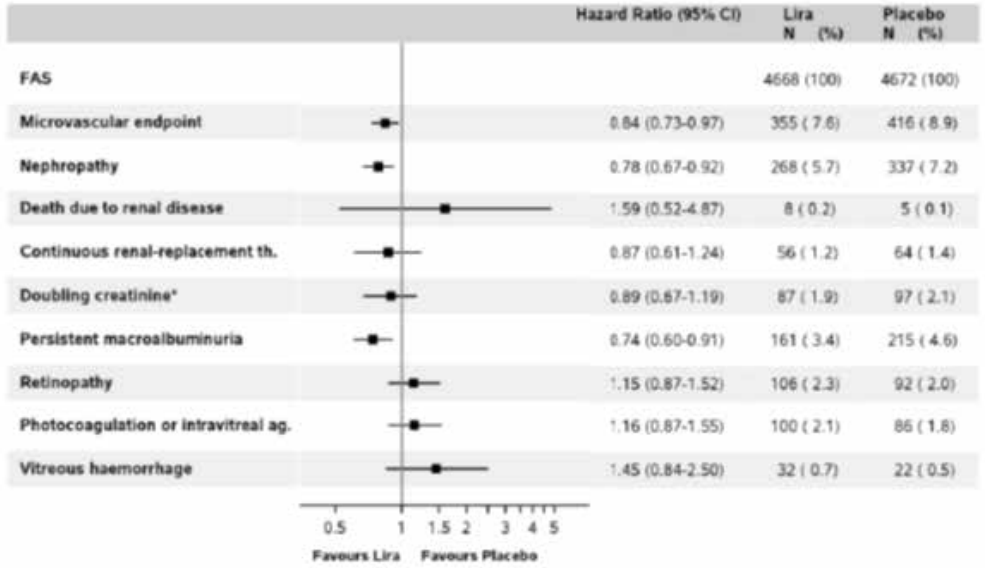


	Hazard Ratio (95% CI)	Lira N (%)	Placebo N (%)
FAS		4668 (100)	4672 (100
Primary MACE	0.87 (0.78-0.97)	608 (13.0)	694 (14.9
Expanded MACE	0.88 (0.81-0.96)	948 (20.3)	1062 (22.7
Components of Expanded MACE:			
Cardiovascular death	0.78 (0.66-0.93)	219 (4.7)	278 (6.0
Non-fatal stroke	0.89 (0.72-1.11)	159 (3.4)	177 (3.8
Non-fatal myocardial infarction	0.88 (0.75-1.03)	281 (6.0)	317 (6.8
Unstable angina pectoris (hospital.)	0.98 (0.76-1.26)	122 (2.6)	124 (2.7
Coronary revascularization	0.91 (0.80-1.04)	405 (8.7)	441 (9.4
Heart failure (hospital.)	0.87 (0.73-1.05)	218 (4.7)	248 (5.3
Other secondary endpoints:			
All cause death	0.85 (0.74-0.97)	381 (8.2)	447 (9.6
Non-cardiovascular death	0.95 (0.77-1.18)	162 (3.5)	169 (3.6

Abbreviations: %: proportion in percent of subjects with an event; CI: confidence interval; FAS: full analysis set;; MACE: major adverse cardiovascular event; Lira: liraglutide; N: number of subjects

Cross-reference: Summary 2.7.4, Appendix 7.1, Figu

Figure 5: Forest plot of the microvascular composite endpoint and its components



Note: Doubling creatinine*: persistent doubling of serum creatinine and eGFR ≤45 mL/min/1.73m^2 per MDRD; Continuous renal-replacement th(erapy): need for continuous renal replacement therapy; Photocoagulation or intravitreal ag(ents): need for retinal photocoagulation or treatment with intravitreal agents. Only 1 subject (in the placebo group) had 1 EAC-confirmed event of 'development of diabetes-related blindness' (Trial 3748 [M5.3.5.1], Table 11-11), therefore, the analysis of the component 'development of diabetes-related blindness' is not included in the figure.

Abbreviations: %: proportion of subjects with an event; CI: confidence interval; FAS: full analysis set; Lira: liraglutide; N: number of subjects; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease.

Cross-reference: Summary 2.7.4, Figure 2-15

Evaluator's comments

Study 3748 (LEADER trial) demonstrates efficacy in this respect, with a risk reduction for MACE of 13% which is clinically as well as statistically significant. Given that diabetes control was also significantly improved in the actively treated group, no conclusion can be drawn regarding the risk reduction being a specific effect of liraglutide as opposed to being a consequence of the improved glycaemic control, or other risk factors such as weight loss or reduction in diastolic BP.

Prevention of cardiovascular events, as it appears in the proposed new statement of indication, is not an 'extension of indication', as stated in the letter of application, but a completely new indication parallel to and separate from that of 'glycaemic control' in the existing statement. The wording of the statement isolates this new indication from the primary indication of use in liraglutide which is to improve glycaemic control in type 2 diabetes mellitus. It reads more like a statement of indication for a cholesterol-lowering or blood pressure reducing drug in type 2 diabetes mellitus.

The sponsor is to be commended for organising the LEADER trial (Study 3748) , whose findings have been much anticipated. However it is stretching interpretation of these findings to introduce prevention of cardiovascular events as a separate indication independent of glycaemic control; reference is made to the introductory statement at the beginning of this section. Study 3748 showed that the subjects experienced an improvement in glycaemic control and a reduction in cardiovascular events. It did not produce any evidence that the second finding was anything other than a consequence of the first, or propose a mechanism where such might be the case as a result of some unique property of liraglutide as distinct from other blood glucose lowering agents.

Separating the two indications has the potential to create situations in which patients might be exposed to risks of unnecessary therapy. A particular and common example would be a patient with type 2 diabetes mellitus who comes under excellent control by the usual criteria as a result of lifestyle measures, with or without the addition of metformin. Should this patient have other risk factors denoting high cardiovascular risk (for example, dyslipidaemia, hypertension), standard of care therapy would demand these be appropriately managed. This new indication would then suggest that the patient should in addition be given liraglutide (Victoza). The risk-benefit analysis as conducted by this evaluation would not support that therapeutic decision, which would in any case be against existing guidelines such as the American Diabetes Association and the European Association for the Study of Diabetes statement already referred to.

The clinical evaluator believed it would be more appropriate for the two indications to be linked, along the lines:

> '*Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control, and to prevent major cardiovascular events when there is associated high vascular risk, as: monotherapy,….. etcetera'.*

Risk management plan

To support the application for Victoza, The sponsor has submitted EU RMP version 27.0 (date 20 October 2016; DLP 30 June 2016) and ASA version 2.1 (date 7 November 2016) (see Table 5 above).

The EU RMP has been updated since the last review with the following potential risks excluded: neoplasms, pancreatic cancer, cardiovascular disorders, immunogenicity in relation to anti-liraglutide antibodies; immunogenicity in relation to immune complex disorders.

The sponsor was requesting an amendment of the condition which requires the PI in the pack for injectables. It proposes to include the CMI in the pack.

There were no objections to the RMP.

Risk-benefit analysis

Discussion

Use as monotherapy

The Delegate agrees with the evaluator that use as restricted monotherapy is approvable. Metformin is current standard of care as unrestricted therapy for type 2 diabetes mellitus. There is no clinical trial demonstrating non inferiority of efficacy and safety over metformin. The Delegate does acknowledge sub-group analysis of the LEADER trial, but this evidence is not robust enough to support this indication. This opinion does not negate the positive efficacy and safety profile the liraglutide has, but rather the limitations of the evidence.

Use for cardiovascular protection

The Delegate agrees with the sponsors comment '*comparative assessment seeking to support consistency in the decision making should be conducted in a manner that takes the following into account: (a) comparability of the study design, (b) magnitude and clinical meaningfulness of the effect size observed supporting the product information claim, and (c) the differential properties exhibited by these various antidiabetic agents used in the*

management of type 2 diabetes mellitus.' This is challenging, as the study designs of the long term cardiovascular benefits of drugs used in type 2 diabetes mellitus are not comparable in relation to patient population or study design, the magnitude of effect may differ due to baseline risk in the patient population and other treatments, and medicine used for diabetes have a range of primary and secondary effects. In addition, the clinical trials for medicines that were approved many years ago like metformin are a very different study design and population as the current trials.

Although there is nonclinical evidence that liraglutide may have an effect independent to its effect on glucose or weight loss in animal models, the data from the LEADER trial was inconclusive in relation to this. The sponsor has performed a number of subgroup analyses of the effects of liraglutide on cardiovascular endpoints when stratified for baseline HbA1c, however of more relevance is the impact of changes in HbA1c due to liraglutide on cardiovascular outcome. Surrogate measures of cardiovascular risk like BP and lipids are not sufficient to give a cardiovascular risk reduction indication.

The sponsor has provided literature in support of anti-inflammatory effects of liraglutide that are independent of cardiometabolic parameters such as weight loss and a reduction in HbA1c. In addition there was evidence of reduced progression of plaque size and inflammation in atherosclerotic animal model that did not occur in a weight matched control group. This is supportive evidence that liraglutide may have an indirect effect on cardiovascular risk.

The difference in HbA1c and BP between the two groups in the LEADER trial, question the blinding and conduct of the study, as physicians were able to use other medicines to reduce cardiovascular risk factors. Patients were seen by investigators in the trial at baseline, 1, 3, 6 months then every 6 months. The dose of insulin at baseline was reduces by 20% in those with HbA1c < 8%, physicians were encouraged to titrate the doses of other medications to achieve HbA1c 7% and BP 130/80mmmHg. The differences in cardiovascular risk profiles between the two arms does provide some support to the efficacy of liraglutide, however it also suggests that the physicians/investigators involved in the trial were not closely titrating patient's medications to achieve optimal parameters. This may increase the external validity of the clinical trial as a similar scenario happens in clinical practice; however it also limits the ability of the study to determine if the effect was due to primary effect of liraglutide.

Perhaps another consideration would be, does it matter if the observed effect was a primary of secondary (due to reduced HbA1c, weight or BP or anti-inflammatory).

Unlike SGLT-2 inhibitors where there is a class effect, the long term safety study for lixisenatide showed non inferiority but not superiority for cardiovascular safety. This study had slightly different patient population (higher cardiovascular risk, younger, shorter duration diabetes, lower HbA1c), but also demonstrated a decrease in -0.4% HbA1c , weight -0.6 kg and BP -0.8 mmHg in the treatment group. Lixisenatide is associated with less increase in heart rate than liraglutide, and has a shorter duration of action. There have been no cardio-protective effects demonstrated for DDP-IV inhibitors.

The EMPA-REG study;[14] enrolled a similar population to that of the LEADER trial; however the outcomes were quite different. The pattern of cardiovascular risk reduction was more clearly defined as death and hospitalisation for heart failure, with a greater risk reduction than in LEADER trial. In the EMPA-REG study there was an initial decrease in HbA1c when the dose of anti-hyperglycaemic therapy was to remain unchanged, followed by a narrowing in the difference in glycaemic control between the two groups; and an early separation of cardiovascular mortality.

[14] Zinman B. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, *N Engl J Med* 2015; 373: 2117-2128

Thus, having considered the LEADER trial,[15] other evidence in support of the effects of liraglutide on inflammation and plaque size, the opinions of the FDA and EU and the clinical evaluator, the Delegate considers that a separate cardiovascular indication is appropriate. The evaluator had concerns that to include a cardiovascular protection indication would widen the patient population to all patients with diabetes, even to those in whom an improvement is not needed. This could be specified in the indication. Not all medicines used for type 2 diabetes mellitus have evidence for cardiovascular protection, the delegate considers it appropriate to differentiate these in the indication as this is an important endpoint for the management of diabetes, and somewhat independent of it's effects on glycaemic control. Although the mechanism behind the cardiovascular risk reduction is somewhat uncertain and may relate to some of the effects of liraglutide on BP or weight reduction or glucose, this does not deny the benefits seen.

The Delegate would suggest the following revised indication:

> *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 contra-indicated or not tolerated*
> - *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
> - *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*
> - *in combination therapy with insulin, with or without metformin.*
>
> *Prevention of cardiovascular events:*
>
> *Victoza is indicated to prevent major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus with poor glycaemic control and at high cardiovascular risk, as an adjunct to standard of care therapy (see Clinical Trials).*

The Delegate supports the replacement of the PI with the CMI and Instructions for use for medicines self-administered by patients, and would welcome the ACM's thoughts on this matter.

Delegate's considerations

1. In relation to unrestricted monotherapy

The sponsor referred to a study comparing liraglutide to glimepiride in patients with type 2 diabetes mellitus. There was no comparison to metformin which is the current standard of care for the initial treatment of type 2 diabetes mellitus. This was previously evaluated at the initial registration of liraglutide and monotherapy not approved. The sponsor is now using the LEADER trial as supportive evidence, however only 3.9% of patients were insulin naïve.

2. In relation to cardiovascular protection

The sponsor has submitted the results of the LEADER trial which demonstrated a reduction in MACE in patients with type 2 diabetes mellitus and high cardiovascular risk. The question is whether this is a separate indication distinct from that of improved

[15] Marso SPet al. Liraglutide and cardiovascular Outcomes in T2DM. *NEJM* 2016; 375: 311-322

glycaemic control, or if the indication should be worded more broadly such as 'the treatment of type 2 diabetes'. The EU and FDA have different views on this.

Proposed action

This medicine is already on the ARTG, the sponsor is proposing a change in indications. The Delegate supports the use liraglutide for restricted monotherapy to improve glycaemic control. The Delegate supports a separate indication in relation to the cardiovascular risk reduction.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACM agree with the use of restricted (rather than unrestricted) mono-therapy?
2. Do the results of the LEADER trial support a separate indication for cardiovascular protection?
3. What are the views of the ACM in relation to having a CMI rather than a PI in the pack for medicines that patients inject themselves?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Changes to indications and/or dosage and administration sections of PI

No changes to the *Dosage and Administration* sections of the PI have been made since the original application in December 2016.

Changes to the Indications have been made for the draft PI submitted with this pre-ACM response. The sponsor accepts the recommendations of the clinical evaluator and Delegate for approval of a 'restricted' monotherapy indication in type 2 diabetes mellitus that is, as monotherapy only when metformin is contraindicated or not tolerated.

The sponsor also accepts, with a minor edit, the recommendation of the Delegate for approval of the prevention of cardiovascular events indication in patients with type 2 diabetes mellitus at high cardiovascular risk with insufficient glycaemic control, see argumentation below.

Sponsor's comments on the delegate's evaluation and proposed action

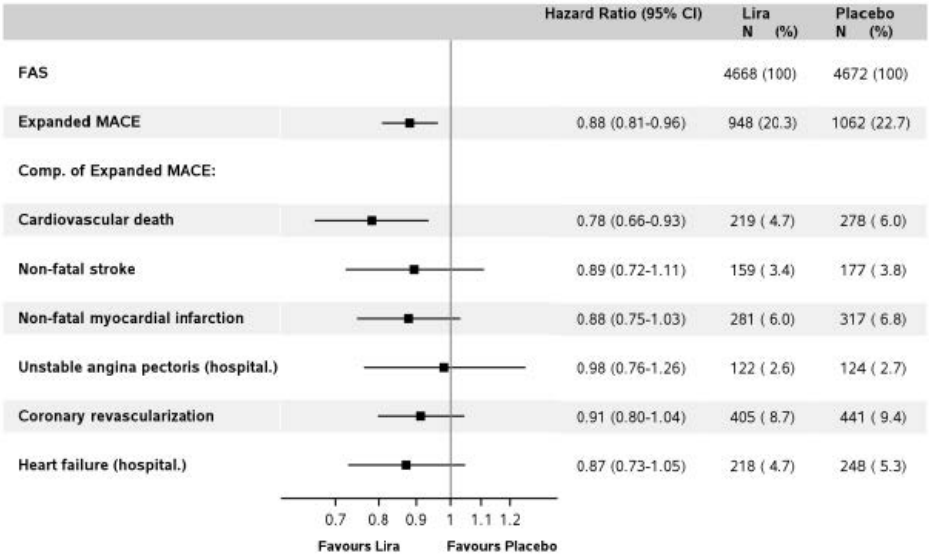
With consistent results across all three components of the primary endpoint, the LEADER trial demonstrated clinically relevant improvements in cardiovascular outcomes with liraglutide compared to placebo, both in addition to standard of care, in individuals at high risk of cardiovascular disease, with a reduction in MACE of 13%. This includes a reduction in cardiovascular deaths of 22%, a reduction of 11% in non-fatal stroke and a reduction of 12% in non-fatal myocardial infarction (Trial 3748, Table 7 and Figure 6). Furthermore, subjects in the liraglutide group had a reduction in all-cause death of 15% (Trial 3748, Table 8).

Table 7: Primary analysis; time to first EAC-confirmed MACE, FAS

		First events			
Treatment	FAS	N	Prop.(%)	Hazard ratio	95% CI
Lira	4668	608	(13.02)		
Placebo	4672	694	(14.85)		
Lira/Placebo				0.868	[0.778 ; 0.968]

MACE: major cardiovascular event, EAC: event adjudication committee.
FAS: full analysis set. CI: confidence interval.
N: number of subjects with a first EAC confirmed event between randomisation date and follow-up date.
Prop: proportion in % of subjects with a first event between randomisation date and follow-up date.
Events which occur before randomisation date are not used for defining first event.
Subjects without an event are censored at time of last contact (phone or visit).

Figure 6: Forest plot of treatment contrast for components of first EAC confirmed expanded MACE



Abbreviations: CI: confidence interval; FAS: full analysis set; Lira: liraglutide; MACE: major adverse cardiovascular event; EAC: event adjudication committee; %: proportion of subjects with an event; N: number of subjects.

Table 8: Secondary analysis; time to EAC confirmed all cause death, FAS

		First events			
Treatment	FAS	N	Prop.(%)	Hazard ratio	95% CI
Lira	4668	381	(8.16)		
Placebo	4672	447	(9.57)		
Lira/Placebo				0.847	[0.739 ; 0.971]

FAS: full analysis set. CI: confidence interval, N: number of subjects with an event between randomisation date and follow-up date, EAC: event adjudication committee.
Prop: proportion in % of subjects with an event between randomisation date and follow-up date.
Events which occur before randomisation date are not used for defining first event.
Subjects without an event are censored at time of last contact (phone or visit).

For comparison, reductions of 25% in the risk of cardiovascular death, myocardial infarction and stroke (The Heart Outcomes Prevention Evaluation);[16] and of 22% in the risk of coronary heart disease and stroke (The Heart Protection Study);[17] have been observed with single antihypertensive or lipid-lowering agents compared to placebo.

[16] HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet*. 2000; 355: 253-259
[17] Collins R, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo controlled trial. *Lancet*. 2003; 361: 2005-2016

These results, obtained more than 10 years ago with the antihypertensive and lipid lowering therapies that were new at the time, showed highly meaningful reductions in cardiovascular risk. The cardiovascular effect of liraglutide was achieved on top of the present standard of care therapies.

Based on previously presented analyses, the sponsor believes that the cardiovascular risk reduction observed with liraglutide in the LEADER trial cannot be fully explained by the improvements in glycaemic control and other risk factors such as body weight, systolic blood pressure, and LDL cholesterol.

Endothelial dysfunction and low grade inflammation are considered early markers of atherosclerosis, and it is well documented that inflammatory mediators play a paramount role in the initiation, progression and stability of atherosclerotic plaques, which ultimately can lead to MACE.[18] As discussed previously the nonclinical data suggest an effect beyond the well-established effect on cardiometabolic parameters. In two different mouse models of atherosclerosis an effect on inflammation in the atherosclerotic plaque area could be demonstrated. In addition, liraglutide has been demonstrated to show favourable changes in markers of endothelial function and inflammation in subjects with type 2 diabetes mellitus;[19,20,21,22] and in two clinical studies intima media thickness was significantly reduced following liraglutide treatment.[23,24]

A number of cardiovascular outcome trials have already been conducted, investigating the potential effect of antidiabetic therapies on cardiovascular safety.[25,26,27,28,29] A reduction in MACE to similar extent as observed in the LEADER trial was only demonstrated for empagliflozin versus placebo,[30] and for canagliflozin versus placebo.[31]

Hence, the results of these cardiovascular outcome trials also reflect differences related to drug properties and the underlying mechanisms of action of these agents. Such differences constitute important knowledge for the prescriber who has to decide on the optimal choice between multiple therapeutic agents, and should therefore be appropriately

[18] Libby P. Inflammation in atherosclerosis. *Nature*. 2002; 420: 868-874
[19] Chen WR et al. Effects of liraglutide on left ventricular function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am Heart J*. 2015; 170: 845-854
[20] Chen WR et al. Effects of liraglutide on left ventricular function in patients with non-ST-segment elevation myocardial infarction. *Endocrine.* 2016; 52: 516-526
[21] von Scholten BJ, et al. Effects of liraglutide on cardiovascular risk biomarkers in patients with type 2 diabetes and albuminuria: A sub-analysis of a randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab*. 2017; 19: 901-905
[22] Plutzky J et al. Reductions in lipids and CV risk markers in patients with type 2 diabetes treated with liraglutide: a meta-analysis. *Can J Diabetes*. 2009; 33: 209-210
[23] Rizvi AA, et al. Liraglutide improves carotid intima-media thickness in patients with type 2 diabetes and non-alcoholic fatty liver disease: an 8-month prospective pilot study. *Expert Opin Biol Ther*. 2015; 15: 1391-1397
[24] Rizzo M, et al. Liraglutide decreases carotid intima-media thickness in patients with type 2 diabetes: 8-month prospective pilot study. *Cardiovasc Diabetol*. 2014; 13: 49
[25] Scirica BM, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326
[26] White WB, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335
[27] Pfeffer MA, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257.
[28] Green JB, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232-42
[29] Holman RR, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017; 77(13):1228-1239
[30] Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-28
[31] Neal B, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017

reflected in the product information to inform the clinical decision on optimal patient care and the management according to the individual patient's specific needs/circumstances.

The sponsor is of the opinion that the LEADER trial data form a scientifically sound and robust basis of evidence, consistent with the requirements specified in the ICH E9 Guideline on Statistical Principles on Clinical Trials and with the regulatory guidelines for cardiovascular outcome trials;[32,33] to support the use of liraglutide for the prevention of cardiovascular disease in patients with type 2 diabetes mellitus. Therefore an additional indication is proposed.

The Australian PI for Jardiance (empagliflozin) includes separate indications for glycaemic control and prevention of cardiovascular events based on the EMPA-REG trial.[14] The sponsor is of the view that the LEADER trial data are at least as robust for the latter indication compared with the EMPA-REG trial, and we contend that a separate cardiovascular indication is therefore also appropriate.

For Victoza, the clinical evaluator recommended a linking of the 'glycaemic control' indication and the 'cardiovascular event prevention' indication due to a concern that Victoza might then be prescribed to subjects with type 2 diabetes mellitus who were in sufficient glycaemic control in order to specifically reduce their cardiovascular risk. The Delegate proposes a modification of the sponsor proposed separate 'cardiovascular event prevention' indication; specifically they propose a restriction to only allow use in subjects with 'poor glycaemic control.' The sponsor accepts the Delegate's recommended indication, but with one minor proposal for change in wording that is, the sponsor proposes the word 'poor' be replaced by 'insufficient'. The LEADER trial design included subjects with HbA1c > 7%, and the sponsor does not consider the word 'poor' to appropriately reflect the level of glycaemic control of all trial subjects. Furthermore, the word 'poor' has other secondary meanings and could be considered stigmatising, whereas 'insufficient' does not in the view of the sponsor have the same unfortunate connotations.

Advisory Committee Considerations[34]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Taking into account the submitted evidence of efficacy, safety and quality, ACM agreed with the Delegate and considered Victoza prefilled multi dose pen for injections containing 6 mg/mL in multi dose pen of 3ml and capable of delivering 0.6 mg, 1.2 mg and 1.8 mg of liraglutide to have an overall positive benefit-risk profile for the proposed indication:

> ***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:*

[32] Food and Drug Administration C. Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Trial Type 2 Diabetes. Dec 2008

[33] European Medicines Agency. Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases (EMA/CHMP/50549/2015). Draft. 21 May 2015

[34] 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.

- *as monotherapy where metformin is not tolerated or contraindicated.*
- *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
- *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*
- *in combination therapy with insulin, with or without metformin.*

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 Clinical Trials).

In making this recommendation, ACM noted:

- the latest EU indications reflect both improving blood sugar and cardiovascular events as integral parts of type 2 diabetes mellitus treatment;
- that many medicines improve glycaemic control but do not improve cardiovascular function.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Does the ACM agree with the use of restricted (rather than unrestricted) monotherapy?*

The ACM agreed with the use of restricted monotherapy.

2. *Do the results of the LEADER trial support a separate indication for cardiovascular protection?*

The ACM stated that the results of the LEADER trial do support a separate indication for cardiovascular protection. ACM noted that a separate indication for cardiovascular protection was previously approved for Jardiance (empagliflozin), which sets somewhat of a precedent. The number needed to treat (NNT) should be included given that modest numbers have been treated so far.

3. *What are the views of the ACM in relation to having a CMI rather than a PI in the pack for medicines that patients inject themselves?*

The ACM discussed the merits of CMI versus PI pack inserts, with an acknowledgement that the PI is generally more written for health professionals and can sometimes be difficult for patients to understand, while the CMI is more user friendly. Although PI documents are not specifically geared to patients, the ACM was of the view that patients should be empowered when it comes to medicines information, and that they should be offered as much relevant information as possible to be informed users. Electronic and digital solutions should also be embraced, with a link to the relevant URL included on printed version.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Victoza liraglutide 6 mg/mL solution for injection 3 mL pre-filled pen for the new indications:

> *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*
>
> *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 CLINICAL TRIALS)*.

The full indication for Victoza 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 CLINICAL TRIALS).*

The full indication for Saxenda liraglutide 6 mg/mL solution for injection is:

> *Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of*
>
> - *≥ 30 kg/m² (obese) or*
> - *≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.*
>
> *Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.*

Specific conditions of registration applying to these goods

- 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 Victoza liraglutide (rys) EU Risk Management Plan (RMP), version 28, dated 11 July 2017, (data lock point 30 June 2016) with Australian Specific Annex, version 3, dated 7 August 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The Consumer Medicines Information (CMI) must be included with the products as a package insert. The CMI should have a link to the full version of the PI on the TGA website.

Attachment 1. Product Information Victoza

The PI for Victoza and Saxenda approved with the submission which is described in this AusPAR is at Attachments 1 and 2 respectively. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Product Information Saxenda

The PI for Saxenda approved with the submission which is described in this AusPAR is at Attachments 1 and 2 respectively. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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