

7.03 LIRAGLUTIDE (rys), injection solution, pre-filled 3 mL pen, 6 mg/mL, 2 and 3 pen packs, Victoza[®], Novo Nordisk Pharmaceuticals

1 Purpose of Application

- 1.1 The submission requested Authority Required (STREAMLINED) listings for liraglutide (rys) for treatment of patients with Type 2 diabetes mellitus and high cardiovascular risk as dual therapy with metformin or a sulfonylurea, triple therapy with metformin and a sulfonylurea, dual therapy with insulin and triple therapy with insulin and metformin.
- 1.2 The submission claimed liraglutide provides a reduction in cardiovascular risk in addition to the reduction achieved by glycaemic control alone (i.e. reduction in HbA1c). However, the submission acknowledged that the mechanism of action by which liraglutide provides cardiovascular benefits in addition to glycaemic control remains unknown (p.137 of the submission).

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with Type 2 diabetes; AND - ≥50 years of age with a history of a prior cardiovascular event; OR - ≥60 years of age at high risk of a cardiovascular event; OR - an Aboriginal and Torres Strait Islander
Intervention	Liraglutide 0.6 mg to 1.8 mg daily by subcutaneous injection, in combination with metformin or a sulfonylurea, metformin and a sulfonylurea or insulin (with or without metformin)
Comparator	Exenatide 10 µg twice daily or 2 mg once weekly by subcutaneous injection
Outcomes	Composite outcome MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); expanded composite cardiovascular outcome: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, hospitalisation for unstable angina pectoris, hospitalisation for heart failure; individual components of the expanded composite cardiovascular outcome; composite microvascular outcome (retinopathy, nephropathy); effectiveness outcomes (HbA1c, body weight, BMI, waist circumference, blood pressure, serum lipids); EQ-5D
Clinical claim	The submission relies on a prior decision of the PBAC which considered liraglutide to be non-inferior to exenatide in terms of reduction in HbA1c in Type 2 diabetes. The current submission claims superiority to exenatide in some patients in terms of reduction in cardiovascular risk, and similar safety.

Source: Constructed during the evaluation

Abbreviations: BMI, body mass index; EQ-5D, EuroQol-5D; HbA1c, glycosylated haemoglobin

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty.	No. of Rpts.	Dispensed Price for Max. Qty.	Proprietary Name and Manufacturer
LIRAGLUTIDE (RYS)			Effective / Published	
Injection, 3 mL pre-filled, multi-dose, disposable pen, 6 mg/mL: 2 pen pack	1	5	\$ [REDACTED] / \$ [REDACTED]	Victoza® Novo Nordisk Pharmaceuticals P/L
Injection, 3 mL pre-filled, multi-dose, disposable pen, 6 mg/mL: 3 pen pack	1	5	\$ [REDACTED] / \$ [REDACTED]	
Category / Program	GENERAL – General Schedule (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Diabetes mellitus type 2			
PBS Indication:	Diabetes mellitus type 2			
Treatment phase:	Dual combination therapy with metformin or a sulfonylurea.			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined			
Treatment criteria:	The treatment must be in combination with metformin. OR: The treatment must be in combination with a sulfonylurea			

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Clinical criteria:	<p>Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR</p> <p>Patient must not have tolerated a combination of metformin and a sulfonylurea,</p> <p>AND</p> <p>Patient must have, or have had, a glycosylated haemoglobin (HbA1c) measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with either metformin or a sulfonylurea.</p> <p>AND</p> <p>The treatment must not be used in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor.</p> <p>AND</p> <p><i>Patient must be 50 years or older with established cardiovascular disease (including at least one of the following: coronary heart disease, prior myocardial infarction, prior stroke or prior transient ischemic attack or peripheral vascular disease) or chronic renal failure (defined as glomerular filtration rate < 60 mL/min/1.73m²) or chronic heart failure (New York Heart Association class II or III); OR</i></p> <p><i>Patient must be 60 years or older with microalbuminuria or proteinuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females); OR</i></p> <p>Patient must be an Aboriginal or Torres Strait Islander</p>
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<p>Prescriber Instructions</p>	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemia and haemoglobinopathies; and/or</p> <p>b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records.</p>
<p>Administrative Advice</p>	<p>Liraglutide is not PBS-subsidised as monotherapy.</p> <p>No increase in the maximum quantity or number of units may be authorised</p> <p>No increase in the maximum number of repeats may be authorised</p>
<p>Condition/Indication:</p>	<p>Diabetes mellitus type 2</p>
<p>Restriction:</p>	<p><input type="checkbox"/> Restricted benefit</p> <p><input type="checkbox"/> Authority Required - In Writing</p> <p><input type="checkbox"/> Authority Required - Telephone</p> <p><input type="checkbox"/> Authority Required - Emergency</p> <p><input type="checkbox"/> Authority Required - Electronic</p> <p><input checked="" type="checkbox"/> Streamlined</p>
<p>Treatment phase:</p>	<p>Triple combination therapy with metformin and a sulfonylurea.</p>
<p>Treatment criteria:</p>	<p>The treatment must be in combination with metformin and a sulfonylurea.</p>
<p>Clinical criteria:</p>	<p>Patient must have a glycosylated haemoglobin (HbA1c) greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea; OR</p> <p>Patient must have, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a two week period prior to initiation of a gliptin, a glitazone or a glucagon-like peptide-1 despite treatment with metformin or a sulfonylurea.</p> <p>AND</p> <p>The treatment must not be used in combination with an insulin, a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor (gliptin).</p> <p>AND</p> <p><i>Patient must be 50 years or older with established cardiovascular disease</i></p>

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	<p>(including at least one of the following: coronary heart disease, prior myocardial infarction, prior stroke or prior transient ischemic attack or peripheral vascular disease) or chronic renal failure (defined as glomerular filtration rate < 60 mL/min/1.73m²) or chronic heart failure (New York Heart Association class II or III); OR</p> <p><i>Patient must be 60 years or older with microalbuminuria or proteinuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females); OR</i></p> <p><i>Patient must be an Aboriginal or Torres Strait Islander</i></p>
Prescriber Instructions	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
Administrative Advice	<p>Liraglutide is not PBS-subsidised as monotherapy.</p> <p>No increase in the maximum quantity or number of units may be authorised</p> <p>No increase in the maximum number of repeats may be authorised.</p>
Condition/Indication:	Diabetes mellitus type 2
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment phase:	Dual combination therapy with insulin
Treatment criteria:	<i>The treatment must be used in combination with insulin</i>
Clinical criteria:	Patient must have, or have had, a glycosylated haemoglobin (HbA1c) measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea; OR

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	<p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with either metformin or a sulfonylurea.</p> <p>AND</p> <p>The treatment must not be used in combination with a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor.</p> <p>AND</p> <p><i>Patient must be 50 years or older with established cardiovascular disease (including at least one of the following: coronary heart disease, prior myocardial infarction, prior stroke or prior transient ischemic attack or peripheral vascular disease) or chronic renal failure (defined as glomerular filtration rate < 60 mL/min/1.73m²) or chronic heart failure (New York Heart Association class II or III); OR</i></p> <p><i>Patient must be 60 years or older with microalbuminuria or proteinuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females); OR</i></p> <p><i>Patient must be an Aboriginal or Torres Strait Islander</i></p>
Prescriber Instructions	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
Administrative Advice	<p>Liraglutide is not PBS-subsidised as monotherapy.</p> <p>No increase in the maximum quantity or number of units may be authorised</p> <p>No increase in the maximum number of repeats may be authorised.</p>

Condition/Indication:	Diabetes mellitus type 2
Restriction:	Authority required (STREAMLINED)
Treatment phase:	Triple combination therapy with insulin and metformin
Treatment criteria:	The treatment must be used in combination with insulin and metformin

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<p>Clinical criteria:</p>	<p>Patient must have, or have had, a glycosylated haemoglobin (HbA1c) measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with either metformin or a sulfonylurea.</p> <p>AND</p> <p>The treatment must not be used in combination with a thiazolidinedione (glitazone), or a dipeptidyl peptidase 4 inhibitor.</p> <p><i>Patient must be 50 years or older with established cardiovascular disease (including at least one of the following: coronary heart disease, prior myocardial infarction, prior stroke or prior transient ischemic attack or peripheral vascular disease) or chronic renal failure (defined as glomerular filtration rate < 60 mL/min/1.73m²) or chronic heart failure (New York Heart Association class II or III); OR</i></p> <p><i>Patient must be 60 years or older with microalbuminuria or proteinuria (defined as urinary albumin excretion rate of >20mcg/min or urinary albumin to creatinine ratio of > 2.5 for males, > 3.5 for females); OR</i></p> <p><i>Patient must be An Aboriginal or Torres Strait Islander.</i></p>
<p>Prescriber Instructions</p>	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor, must be documented in the patient's medical records.</p>
<p>Administrative Advice</p>	<p>Liraglutide is not PBS-subsidised as monotherapy.</p> <p>No increase in the maximum quantity or number of units may be authorised</p> <p>No increase in the maximum number of repeats may be authorised.</p>

- 2.2 In the PSCR (p.1) the sponsor proposed revisions to the PBS restriction and pricing for liraglutide 1.2 mg/day. The sponsor requested progressing the recommendation from the PBAC in March 2013 for Victoza® 1.2 mg/day (2 pen pack): DPMQ \$ [REDACTED]. The ESC noted the March 2013 recommendation did not include combination use with insulin.
- 2.3 Prior to March 2013, the submissions for liraglutide did not present any efficacy data for liraglutide 1.2 mg daily as the submissions assumed that liraglutide 1.2 mg/day was a titration dose and all patients would up-titrate to 1.8 mg/day based on Study 1797 (LEAD-6). The March 2013 re-submission assumed that the most common dose of liraglutide would be 1.2 mg/day based on German usage data. In this resubmission, the dose in the LEADER trial was titrated to 1.8 mg, with 84.8% of patients exposed to 1.8 mg.
- 2.4 In the PSCR (p.1) the sponsor proposed revisions to the PBS restriction and pricing for liraglutide 1.8 mg/day (3 pen pack): DPMQ \$ [REDACTED] (1.5 × ex-manufacturer price for the 1.2 mg/day dose) for patients with T2DM at high cardiovascular (CV) risk. The ESC was uncertain whether the progression of 1.2 mg/day recommendation would go ahead regardless of the outcome for the 1.8 mg/day proposed restriction and how the different restrictions by strength could be implemented in clinical practice. The Pre-PBAC response (p.1) indicated the 1.2 mg/day listing would go ahead alongside 1.8 mg/day and having both doses available would meet the clinical need for T2DM patients.
- 2.5 The ESC considered the proposed restrictions to be complex and unworkable with incentive to send patients for unnecessary tests and exclusion of patients who may benefit. The restriction would be difficult to implement in practice. Although the trial was for a highly selected population, it is unclear whether other patients would benefit; particularly younger patients or those with undiagnosed CV disease. Inclusion of age criteria may be inappropriate, especially for patients with symptomatic CV disease.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Liraglutide (Victoza®) was registered on the Australian Register of Therapeutic Goods (ARTG) on 28 August 2010 as an adjunct to diet and exercise for the treatment of adults with Type 2 diabetes mellitus to achieve glycaemic control in dual combination therapy with metformin or a sulfonylurea, triple combination therapy with metformin and a sulfonylurea, and in combination therapy with basal insulin, with or without metformin. Liraglutide (Saxenda®) is also registered on the ARTG as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients.

- 3.2 A TGA application for an extension of the current liraglutide indication to include the treatment of patients with Type 2 diabetes and high cardiovascular risk was submitted on 31 October 2016 and will be considered at the December 2017 Advisory Committee on Medicines meeting. TGA documents were not available during the evaluation. The ESC advised the concurrent review of the pivotal evidence presented in the LEADER trial is of relevance to the PBAC. The PBAC agreed the outcome of the TGA evaluation will be informative.
- 3.3 Liraglutide has been considered by the PBAC for use in Type 2 diabetes on five previous occasions (November 2010, July 2011, November 2011, March 2013, November 2015), and liraglutide 1.2 mg once daily was recommended for listing on the basis of non-inferiority to exenatide 10 µg twice daily in dual combination therapy with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea at the March 2013 meeting. Liraglutide was not listed on the PBS.
- 3.4 The PBAC has not previously considered submissions for the requested restriction; patients with Type 2 diabetes with high cardiovascular risk.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Population and disease

- 4.1 Type 2 diabetes is a long term progressive metabolic disorder caused by resistance to the glucose modulating effects of insulin in body tissues and/or gradual loss of capacity to produce sufficient insulin. Type 2 diabetes is associated with strong familial and lifestyle risk factors. Long terms complications include heart disease, stroke, diabetic retinopathy which may lead to blindness, diabetic nephropathy which may lead to end stage renal failure and peripheral vascular disease which may lead to amputation. Type 2 diabetes substantially increases the risk of cardiovascular disease, cardiovascular mortality and chronic kidney disease leading to end stage renal failure.
- 4.2 The submission proposed that liraglutide would offer an alternative to exenatide within the current clinical management algorithm.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated exenatide as the main comparator. This is an appropriate comparator. However, empagliflozin (registered for use in patients with type 2 diabetes and established cardiovascular disease) or other listed diabetes medicines likely to be substituted with liraglutide may also be appropriate secondary comparators. The PSCR (p.2) argued that empagliflozin is not an appropriate comparator as it has a different mechanism of action and that empagliflozin is listed

on the PBS for glycaemic control and not CV outcomes. The ESC considered empagliflozin prescribing may target the same patient group proposed for 1.8 mg/day liraglutide despite not having a specific PBS listing and is a relevant comparator given it offers similar reductions in direct CV outcomes across the broader Type 2 diabetes population at a substantially lower price.

- 5.2 Exenatide clinical trial data relevant to the requested restriction could not be identified for the submission. Therefore, placebo was used as a proxy for exenatide treatment effects in the clinical comparison and the economic analysis, assuming exenatide provided no difference in reduction in cardiovascular risk for patients with Type 2 diabetes compared to placebo. The absence of evidence of exenatide providing cardiovascular benefits to patients with Type 2 diabetes is not evidence of no treatment effect and the ESC considered the use of placebo as a proxy for exenatide was not appropriate. The exenatide EXSCEL cardiovascular outcomes trial (exenatide 2 mg once weekly subcutaneous injection versus placebo (standard care)), expected to be completed in April 2018, may be informative to the comparison with liraglutide.
- 5.3 The PSCR (pp.2-3) highlighted four meta-analyses of Type 2 diabetes RCT safety data showed no statistically significant differences for exenatide versus placebo in cardiovascular outcomes, and therefore the use of placebo as a proxy for exenatide treatment effect was reasonable. The ESC noted three of the same four meta-analyses included liraglutide, and similarly showed no statistically significant differences for liraglutide versus placebo in cardiovascular outcomes (see table below). The PSCR further referenced the top line results from the EXSCEL trial from a 23 May 2017 press release and stated that exenatide did not meet the efficacy objective of a superior reduction in MACE and therefore demonstrated no reduction in CV risk with exenatide. The ESC noted the EXSCEL trial press release stated although statistical significance was not reached, there were fewer CV events observed with exenatide. A formal indirect comparison is unable to be performed without further publication of EXSCEL trial patient characteristics and trial results.

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Table 2: Meta-analyses of randomised controlled trials of GLP-1 receptor agonists versus placebo in patients with Type 2 diabetes mellitus reporting MACE outcomes

Citations	GLP-1s included	Primary outcomes	Number of trials (patients) pooled	GLP-1 vs placebo Ratio (95% CI)
Ferdinand 2016	<u>Dulaglutide</u> 0.75 mg or 1.5 mg once weekly (Phase III); 0.1 mg to 3 mg (Phase II)	MACE+ (unstable angina)	6 Phase II/III studies (4588 patients) Study durations: 12-104 weeks	MACE+: Hazard ratio <u>Dulaglutide</u> : 0.47 (0.09, 2.57), p=0.30
Fisher 2015	<u>Albiglutide</u> 15 mg, 30 mg or 50 mg once weekly, or 30 mg twice daily	MACE + unstable angina	5 Phase II/III studies (1604 patients) Study durations: 16 weeks (Phase II) or 3 years (Phase III)	MACE (excluding unstable angina): Hazard ratio <u>Albiglutide</u> = 0.69 (0.35, 1.35), p=0.28
Monami 2014	<u>Exenatide</u> 5 µg or 10 µg twice daily <u>Liraglutide</u> 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg once daily <u>Taspoglutide</u> 10 mg or 20 mg once weekly	MACE	<u>Exenatide</u> : 6 Phase II/III studies (1864 patients) <u>Liraglutide</u> : 5 Phase III studies (3024 patients) <u>Taspoglutide</u> : 1 Phase III study (368 patients) Study duration: 24-30 wks	MACE: Odds ratio <u>Exenatide</u> : 0.45 (0.20, 1.02) <u>Liraglutide</u> : 0.60 (0.22, 1.62) <u>Taspoglutide</u> : 0.50 (0.03, 8.06)
Ratner 2011	<u>Exenatide</u> 2.5 µg, 5 µg or 10 µg twice daily	Expanded MACE	8 Phase II/III studies (2583 patients) Study durations: 12-52 weeks	Expanded MACE: <u>Exenatide</u> : 0.53 (95% CI NR)
Seshasai 2015	<u>Taspoglutide</u> 10 mg or 20 mg once weekly	Expanded MACE	4 Phase III studies (3106 patients) Study durations: ~1 year	Expanded MACE: Odds ratio <u>Taspoglutide</u> : 1.13 (0.53, 2.43)
Sun 2012	<u>Exenatide</u> 10 µg or 20 µg twice daily, 2 mg once weekly <u>Liraglutide</u> 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg once daily <u>Albiglutide</u> 4 mg, 15 mg or 30 mg once weekly, 15 mg, 30 mg, or 50 mg twice weekly, 50 mg or 100 mg four times weekly <u>Taspoglutide</u> 5 mg, 10 mg, 20 mg, 30 mg or 40 mg once weekly, 10 mg or 20 mg twice daily <u>Lixisenatide</u> 5 µg, 10 µg, 20 µg or 30 µg (once or twice daily) <u>Dulaglutide</u> 0.5 mg, 1 mg or 2 mg once weekly	Cardiovascular mortality, ischemic heart disease, myocardial infarction, stroke	<u>Exenatide</u> : 15 Phase II/III studies (3500 patients) <u>Liraglutide</u> : 9 Phase II/III studies (3185 patients) <u>Albiglutide</u> : 1 Phase II study (311 patients) <u>Lixisenatide</u> : 1 Phase II study (542 patients) <u>Taspoglutide</u> : 2 Phase II studies (326 patients) <u>Dulaglutide</u> : 1 Phase II study (262 patients) Study durations: 8-104 weeks	Cardiovascular events: Odds ratio (network meta-analysis): <u>Exenatide</u> : 0.53 (0.23, 1.24); 0.84 (0.4, 1.57) <u>Liraglutide</u> : 0.86 (0.36, 2.31); 0.79 (0.37, 1.53) <u>Albiglutide</u> : 2.57 (0.14, 46.34); 1.05 (0.14, 4.32) <u>Lixisenatide</u> : 0.25 (0.01, 12.80); 23.21 (0, 70.53) <u>Taspoglutide</u> : 0.92 (0.08, 10.27); 0.44 (0.08, 33.33) <u>Dulaglutide</u> : 0.34 (0.01, 17.22); 136.20 (0, 408.00)

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Wang 2016 ^a	<u>Exenatide</u> 10 µg 20 µg twice daily, 2 mg once weekly <u>Liraglutide</u> 0.6 mg, 0.9 mg, 1.2 mg, 1.8 mg once daily <u>Albiglutide</u> 30 mg or 50 mg once weekly <u>Lixisenatide</u> 20 µg once daily	MACE + fatal myocardial infarction, fatal stroke	Phase III and IV trials <u>Exenatide</u> : 13 trials (4135 patients) <u>Liraglutide</u> : 7 trials (4161 patients) <u>Albiglutide</u> : 6 trials (3588 patients) <u>Lixisenatide</u> : 6 trials (8215 patients) Study durations (median): 24-156 weeks	MACE+: Odds ratio <u>Exenatide</u> : 0.12 (0.00, 6.07); 0.45 (0.02, 8.74) <u>Liraglutide</u> : NA; 1.92 (0.45, 8.08); 2.29 (0.36, 14.66) <u>Albiglutide</u> : NA; 0.60 (0.19, 1.90); 0.25 (0.06, 1.08) <u>Lixisenatide</u> : 1.00 (0.09, 11.05); 7.31 (0.15, 368.62); 2.74 (0.38, 19.50)
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Source: Table C.4.7, pp.132-133 of the submission

Abbreviations: GLP-1, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular events; NR, not reported

^a Meta-analyses included dulaglutide, but no CV outcomes data were reported

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC inquired to whether the cardiovascular outcomes demonstrated with liraglutide is likely to be class effect across the Glucagon-Like Peptide-1 (GLP-1) analogues. The clinician stated that liraglutide's unique molecular structure may contribute the different effect not yet observed with exenatide, however the clinician agreed there may be a class effect that is yet to be seen. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with liraglutide most notably the reduced risk of cardiovascular mortality and lower risk of hypoglycaemia.

6.3 The PBAC noted the advice received from Diabetes Australia and The Australian Diabetes Society clarifying the likely use of liraglutide in clinical practice. The consumer comments noted liraglutide has been shown to reduce the risk of cardiovascular mortality. It was also noted that three medications that do not cause weight gain, and that lower circulating insulin and glucose without risk of hypoglycaemia have been shown to reduce cardiovascular events (liraglutide, empagliflozin, and metformin). The PBAC noted that this advice was generally supportive of the evidence provided in the submission.

Clinical trials

6.1 The submission is based on one head-to-head direct cardiovascular outcomes trial comparing liraglutide to placebo (LEADER). The ESC noted the LEADER trial was designed to examine cardiovascular safety rather than cardiovascular protective effect.

6.2 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
LEADER	Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER). A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events. (NCT01179048) Marso, S.P., et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes	Date 29 August 2016 <i>New England Journal of Medicine</i> 2016; 375(4): 311-322
FREEDOM-CVO	Press release: http://www.intarcia.com/media/press-releases/2016-may-6-cardiovascular-safety.html (NCT01455896)	Unpublished

Source: Table B.2.4, p.58 of the submission

6.3 The submission identified one potentially relevant unpublished exenatide trial (FREEDOM-CVO), but results were not available and the trial used an experimental formulation of exenatide (ITCA 650) not available Australia. The literature review also identified the exenatide EXSCEL cardiovascular outcomes trial, but this trial is yet to be completed. The ESC noted the FREEDOM-CVO trial appeared to be designed to assess cardiovascular safety rather than cardiovascular protective effect.

6.4 On the basis of a press release stating that the experimental formulation of exenatide demonstrated non-inferior cardiovascular safety compared to placebo in the FREEDOM-CVO trial, the placebo arm of the LEADER trial was used as a proxy for exenatide treatment effects in the clinical comparison and the economic analysis of the submission.

6.5 The inclusion of FREEDOM-CVO was not appropriate, given this formulation is not used in current clinical practice and no evidence of the comparative efficacy and safety of ITCA 650 versus placebo or versus exenatide twice daily and once weekly was provided. The assumption that exenatide provides no additional reduction in cardiovascular risk in Type 2 diabetes compared to placebo was inadequately supported, and the use of the LEADER placebo arm as a proxy for an exenatide treatment arm was not appropriate. The results of the placebo comparison were evaluated in the commentary.

6.6 The key features of the direct randomised trials are summarised in the table below.

Table 4: Key features of the included evidence, liraglutide (once daily) versus exenatide 10 µg (twice weekly)

Trial	Design/ duration of follow-up	N	Compared interventions	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
LEADER	R, DB, PC, MC FAS 3.5-5 years	4672 4768	Liraglutide 0.6 - 1.8 mg once weekly subcutaneous injection + standard care; ^c versus Placebo (standard care) ^c	Low	≥ 50 years with ≥1 CV event; or ≥60 years with high CV risk. HbA1c ≥ 7%	MACE ^a and components, microvascular, all-cause mortality, non-CV mortality, HbA1c, EQ-5D	Yes
FREEDOM-CVO	R, DB, PC, MC	4156	ITCA 650 60 µg daily continuous subcutaneous infusion; versus Placebo (standard care) ^d	NR	≥ 40 years with ≥ 1 CV event; or ≥ 60 years with high CV risk; HbA1c ≥ 6.5%	MACE ^b (not reported)	No
EXSCEL	R, DB, PC, MC	14000	Exenatide 2 mg once weekly subcutaneous injection; versus Placebo (standard care) ^d	NR	≥ 18 years. HbA1c ≥ 6.5% < 10%	MACE ^a (not completed)	No

Source: Table B.2.3, p.57 of the submission; Study record details for EXSCEL (NCT01144338) accessed 27 March 2017 from <https://clinicaltrials.gov/ct2/show/record/NCT01144338?term=exscele&rank=1>

Abbreviations: DB, double blind; EQ-5D, EuroQol-5D; FAS, full analysis set; HbA1c, glycosylated haemoglobin; MACE, major adverse cardiovascular events; MC, multi-centre; PC, placebo controlled; R, randomised.

^a Composite MACE outcome composed of cardiovascular death, non-fatal MI, non-fatal stroke

^b Composite MACE outcome composed of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina

^c Standard care included concomitant diabetes medicines (primarily metformin, sulfonylurea and insulin) required to maintain glycaemic control and cardiovascular medicines.

^d Standard care included concomitant diabetes medicines (not specified) required to maintain glycaemic control and cardiovascular medicines.

6.7 The inclusion criteria in the LEADER trial were similar to the high cardiovascular risk criteria used in the requested restriction. However, there were differences with Australian clinical practice (exclusion of patients with recent GLP-1 receptor agonist or DPP4 inhibitor use; small proportions of patients aged over 60 years despite best practice guidelines recommending all patients with Type 2 diabetes aged over 60 years be considered at high risk). The ESC considered that some patients who may benefit from treatment with liraglutide will be excluded by criteria that restrict treatment to those over 50 with diabetes and established cardiovascular disease whilst Aboriginal and Torres Strait Islander people are included at any age. The ESC also noted the inclusion of radiological rather than symptomatic cardiovascular disease may provide incentive for otherwise unnecessary radiological investigation in the over 60 group.

6.8 The LEADER trial used the MACE composite outcome (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), expanded MACE composite outcome and a microvascular composite outcome (first nephropathy event, need for continuing renal dialysis, first retinopathy event) comparing liraglutide with placebo. MACE included appropriate patient relevant cardiovascular outcomes, but the

microvascular composite outcome included both procedural and patient relevant outcomes.

Comparative effectiveness

6.9 The primary composite MACE outcome and component outcomes of the LEADER trial are presented in Table 5 and Figure 1 below.

Table 5: Time to first EAC-confirmed MACE and component events over 60 months (FAS)

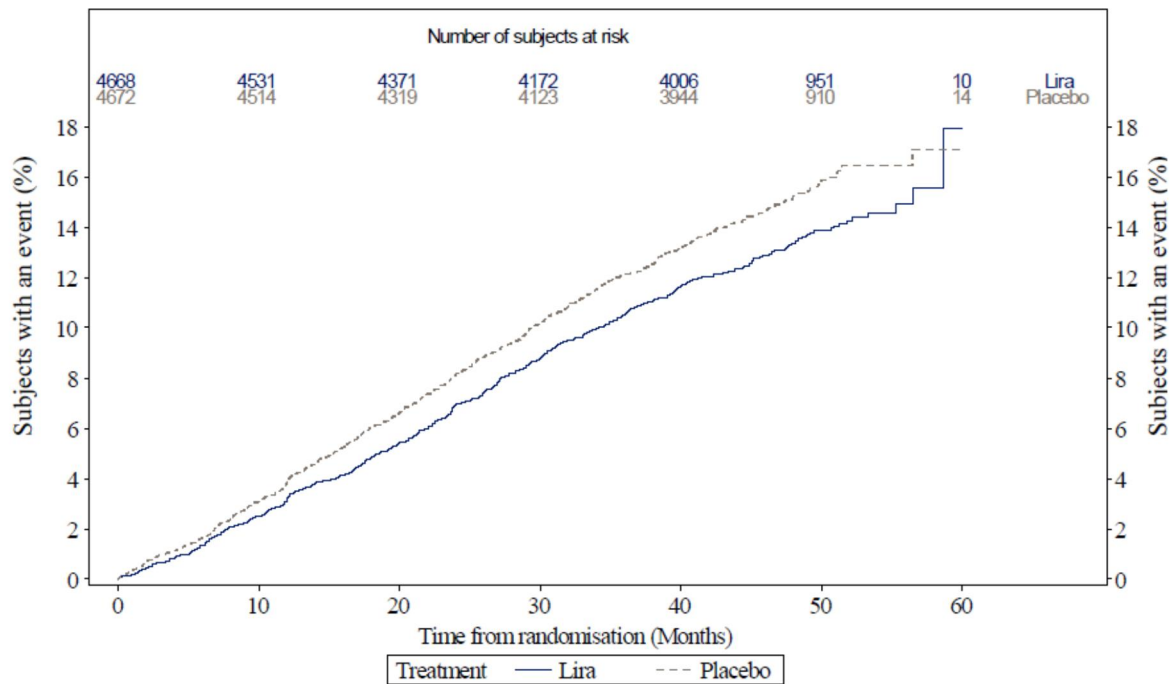
Trial ID	Liraglutide N=4668		Placebo N=4672		Hazard ratio ^c (95% CI)
	n with events (%)	Events per 100 patient years ^a	n with events (%)	Events per 100 patient years ^b	
MACE	608 (13.02%)	3.41	694 (14.85%)	3.91	0.868 (0.778, 0.968)
Component outcomes (MACE)^d					
Cardiovascular death	219 (4.7%)	1.23	278 (6.0%)	1.57	0.78 (0.66, 0.93)
Non-fatal myocardial infarction	281 (6.0%)	1.58	317 (6.8%)	1.79	0.89 (0.72, 1.11)
Non-fatal stroke	159 (3.4%)	0.89	177 (3.8%)	1.00	0.88 (0.75, 1.03)
Mortality outcomes					
All-cause death	381 (8.2%)	2.14	447 (9.6%)	2.52	0.847 (0.739, 0.971)
Non-cardiovascular death	162 (3.5%)	0.91	169 (3.6%)	0.95	0.952 (0.768, 1.181)
Time to first microvascular event	355 (7.6%)	1.99	416 (8.9%)	2.34	0.84 (0.73, 0.97)
First nephropathy event ^d	268 (5.7%)	1.50	337 (7.2%)	1.90	0.78 (0.67, 0.92)
Need continuing dialysis	56 (1.2%)	0.34	64 (1.4%)	0.4	0.87 (0.61, 1.24)
Death due to renal disease	8 (0.2)	0.04	5 (0.1)	0.03	1.59 (0.52, 4.87)
First retinopathy event	106 (2.3%)	0.59	92 (2.0%)	0.52	1.15 (0.87, 1.52)

Source: Tables B.6.2, p.81, B.6.3, p.83, B.6.4, p.84, B.6.6, p.88 and B.6.13, p.100 of the submission. Statistically significant results in bold
Abbreviations: EAC, evaluation adjudication committee; FAS, full analysis set; MACE, major adverse cardiac event

^a 17822 patient years of observations; ^b 17741 patient years of observations; ^c Results >1 favour placebo. Results <1 favour liraglutide;

^d Analysis independent of the composite outcome

Figure 1: Kaplan Meier plot of time to first EAC confirmed MACE (FAS)



Source: Figure B.6.1, p.82 of the submission

Abbreviations: EAC, event adjudication committee; FAS, full analysis set; Lira, liraglutide; MACE, major adverse cardiac event

- 6.10 Liraglutide was associated with a 13.2% reduction in risk of a major adverse cardiovascular event compared to placebo (HR 0.868, 95% CI [0.778, 0.968]). A similar reduction in risk was observed for the time to expanded MACE composite outcome (HR 0.881, 95% CI [0.807, 0.962]).
- 6.11 Component outcomes occurred in smaller proportions of patients treated with liraglutide compared to placebo (standard care), with statistically significant differences in reduction in risk of cardiovascular death and all-cause death favouring liraglutide. The statistically significant reductions in overall cardiovascular risk observed in the MACE and expanded MACE composite outcomes for patients treated with liraglutide appeared to be primarily driven by the reduction in risk of cardiovascular death.
- 6.12 In post-hoc analyses undertaken for Marso et al. (2016), smaller proportions of patients treated with liraglutide experienced cardiovascular events compared to placebo, but only risk of “all myocardial infarction” (one or more fatal, nonfatal or silent infarct events) reached borderline statistical significance (HR 0.86; 95% CI [0.73, 1.00]). This analysis should be interpreted with caution given differences in the severity and disability between events, and between single or multiple events in individual patients.
- 6.13 Time to first microvascular event was statistically significantly in favour of liraglutide and was solely driven by microvascular nephropathy events which occurred in smaller proportions of patients treated with liraglutide, with a statistically significant reduction in risk of 16% compared to placebo. There was no statistically significant

difference in nephropathy requiring continuing renal dialysis between treatment arms.

- 6.14 It is unclear whether reductions in cardiovascular events observed in LEADER were related to treatment with liraglutide alone or in some part to higher rates of glycaemic control compared with placebo. The PSCR (p.1) highlighted that landmark RCT (UKPDS, ADVANCE, ACCORD, VADT) comparing intense glucose lowering vs standard care up to 10 years showed HbA1c reductions of >1% without significant reductions in cardiovascular outcomes. The ESC noted the mechanism of action of liraglutide on CV outcomes is unclear. In the NEJM article¹ it is hypothesised that the time taken for a significant reduction in CV outcomes to be seen, which is longer in the LEADER trial than in the empagliflozin EMPA-REG OUTCOME trial¹, may be due to an effect on the development of atherosclerosis rather than a haemodynamic effect.
- 6.15 The differences between treatment arms in glycaemic control are summarised in Table 6.

Table 6: Supportive analyses – glycaemic control outcomes

	Liraglutide N=4668		Placebo N=4672		Difference
	Mean baseline	Mean change	Mean baseline	Mean change	Mean difference (95% CI)
HbA1c (%)					
HbA1c (%); mean change to 36 months	8.7	-1.161	8.7	-0.765	-0.396 (-0.453, -0.338)
HbA1c (%); mean change to end of treatment	8.7	-0.967	8.7	-0.685	-0.290 (-0.351, -0.230)
Proportion of HbA1c responders (HbA1c <7%)	n (%)		n (%)		Mean difference (95% CI)
HbA1c responders at 36 months	1865 (40.0%)		1139 (24.4%)		NR
HbA1c responders at end of treatment	1605 (34.4%)		1074 (23.0%)		NR

Source: Table B.6.8, p.94 of the submission and Tables 11-14 and 11-15, pp.258-259 of the LEADER Clinical Trial Report

Statistically significant results in bold

Abbreviations: HbA1c, glycosylated haemoglobin; NR, not reported

- 6.16 Patients treated with liraglutide achieved statistically significantly larger reductions in HbA1c compared to placebo, and larger proportions of patients treated with liraglutide achieved glycaemic control (HbA1c <7.0%). However, only one in four patients treated with placebo (standard care) achieved glycaemic control, and at 36 months the mean HbA1c for placebo patients was more than 7.9%. Differences in glycaemic control between patients treated with liraglutide and standard care may have been related to differences in diabetes treatment intensification protocols in the LEADER trial. The ESC noted that patients in the placebo arm received higher dose of insulin.
- 6.17 The secondary outcome of patient reported hypoglycaemia events in the LEADER trial are presented in Table 7 below.

¹ N Engl J Med 2016; 375:311-322 [July 28, 2016](https://doi.org/10.1056/NEJMoa1603827) DOI: 10.1056/NEJMoa1603827

Table 7: Patients reporting hypoglycaemic events (FAS; MMRM)

Trial ID	Liraglutide N=4668			Placebo N=4672		
	n (%)	Events	Events per 100 patient years ^a	n (%)	Events	Events per 100 patient years ^b
Confirmed hypoglycaemia event	2039 (43.7%)	12,177	70.2	2130 (45.6%)	15,756	91.2
Severe hypoglycaemia	114 (2.4%)	178	1.0	153 (3.3%)	255	1.5
Symptomatic hypoglycaemia	2409 (51.6%)	26,514	152.9	2431 (52.0%)	34,322	198.6
Asymptomatic hypoglycaemia	2479 (53.1%)	25,131	144.9	2360 (50.5%)	25,823	149.4
Probable hypoglycaemia	148 (3.2%)	300	1.7	148 (3.2%)	259	1.5

Source: Table B.6.17, p.103 of the submission

Abbreviations: FAS, full analysis set; MMRM, mixed model for repeated measurement

^a 17822 patient years of observations; ^b 17741 patient years of observations

6.18 Similar proportions of patients treated with liraglutide reported severe hypoglycaemia events compared to placebo. However, there were fewer severe hypoglycaemia events overall in the liraglutide arm compared to placebo (estimated rate ratio 0.689, 95% CI [0.514, 0.925]). The ESC agreed that this was important given that patients taking liraglutide had lower HbA1c and would therefore expect higher incidence of hypoglycaemia events.

6.19 The analysis of severe hypoglycaemia events presented in the submission may have been skewed by outliers with poor glycaemic control contributing large numbers of events. In addition, given the exclusion of concomitant DPP4 and SGLT2 inhibitors in the LEADER trial at trial entry and differences in insulin and sulfonylurea utilisation between the liraglutide and placebo treatment arms these results may not be applicable to the eligible Australian population.

6.20 Table 8 summarises the results of the EQ-5D questionnaire, conducted at selected sites in the LEADER trial.

Table 8: Mean change in EQ-5D from baseline to 36 months/end of treatment (selected sites)

Trial	Liraglutide (N=1523)			Placebo (N=1534)			Mean difference (95% CI)
	Reporting n (%)	Baseline EQ-5D (SD)	Mean change EQ-5D	Reporting n (%)	Baseline EQ-5D (SD)	Mean change EQ-5D	
LEADER	1496 (98.2%)	0.8 (0.2)	-0.027	1500 (97.8%)	0.8 (0.2)	-0.046	0.018 (0.001, 0.035)

Source: Table B.6.7, p.91 of the submission. Statistically significant results in bold

Note: EQ-5D data from 10/32 selected sites only - Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, UK and USA

6.21 The difference in mean change in EQ-5D from baseline was statistically significant in favour of liraglutide, but the difference was small and may not be clinically important.

Comparative harms

6.22 The proportions of patients reporting any adverse event, serious adverse events or medical events of special interest (MESI) were similar between liraglutide and placebo (standard care). More deaths were reported in patients treated with

placebo compared to liraglutide, consistent with the proportions of cardiovascular deaths observed in the primary composite outcome (MACE). Statistically significantly larger proportions of patients treated with liraglutide reported adverse events leading to discontinuations.

- 6.23 The adverse events most commonly reported by patients treated with liraglutide were gastrointestinal events (nausea, vomiting, gastric motility disturbances, gallbladder disease, thyroid disease) and cardiovascular events (unstable angina, acute myocardial infarction, cardiac failure - not defined) consistent with the LEADER inclusion criteria and the requested restriction. The proportions of patients reporting EAC-confirmed pancreatitis were small for both liraglutide and placebo.
- 6.24 The reported adverse events in the LEADER trial were consistent with those reported in the broader populations previously considered by the PBAC (liraglutide PSD November 2010, November 2011 and March 2013). However, the proportions of patients reporting all events were substantially smaller in the LEADER trial.
- 6.25 The Product Information document advises that liraglutide is contraindicated in patients with a history of GLP-1 analogue associated pancreatitis, and recommends caution with use in renal impairment, thyroid disease, pancreatitis and hypoglycaemia in combination with other diabetes medicines.
- 6.26 The PBAC previously considered liraglutide 1.2 mg once daily to be non-inferior to exenatide 10 µg twice daily in terms of safety when used as dual combination therapy with metformin or a sulfonylurea, and as triple combination therapy with metformin and a sulfonylurea (March 2013 liraglutide PSD, paragraph 12).

Benefits and harms

- 6.27 A summary of the comparative benefits and harms for liraglutide versus placebo is presented in the table below.

Table 9: Summary of comparative benefits and harms for liraglutide versus placebo

Benefits n with events (%)				
Event	Liraglutide n with events (%)	Placebo n with events (%)	Absolute difference	HR (95% CI)
Major adverse cardiovascular event	608/4668 (13.0%)	694/4672 (14.9%)	1.9%	0.87 (0.78, 0.97)
Cardiovascular death	219/4668 (4.7%)	278/4672 (6.0%)	1.3%	0.78 (0.66, 0.93)
All-cause death	381/4668 (8.2%)	447/4672 (9.6%)	1.4%	0.85 (0.74, 0.97)
Time to first microvascular event	355/4668 (7.6%)	416/4672 (8.9%)	1.3%	0.84 (0.73, 0.97)
Severe hypoglycaemia events	114/4668 (2.4%)	153/4672 (3.3%)	0.9%	NR
Harms				
Adverse event	Liraglutide n with events (%)	Placebo n with events (%)	Absolute difference	RR (95% CI)
Nausea	175/4668 (3.7%)	44/4672 (0.9%)	2.8%	NR
Vomiting	97/4668 (2.1%)	24/4672 (0.5%)	1.6%	NR
Gastrointestinal motility disorders	140/4668 (3.0%)	63/4672 (1.3%)	1.7%	NR

Source: Tables B.6.9, p.96, B.6.16, p.102 and Figure B.6.11, p.98, of the submission

NOTE: It may not be reasonable to extrapolate ratios of patients experiencing events during the trial period beyond 42 months

6.28 For every 100 patients treated with liraglutide compared with placebo (over 42 months) there would be:

- Approximately 2 fewer patients experiencing a major cardiovascular event;
- Approximately 1 fewer patient experiencing cardiovascular death;
- Approximately 1 fewer patient experiencing death from any cause;
- Approximately 1 fewer patient experiencing a microvascular nephropathy event; and
- Approximately 1 fewer patient experiencing a severe hypoglycaemia event.

6.29 For every 100 patients treated with liraglutide compared with placebo (over 42 months) there would be:

- Approximately 3 additional patients experiencing nausea;
- Approximately 2 additional patients experiencing vomiting; and
- Approximately 2 additional patients experiencing gastrointestinal motility disorder.

Clinical claim

6.30 The submission noted that liraglutide was considered to be non-inferior to exenatide 10 µg twice daily in terms of glycaemic control and safety by the PBAC at the March 2013 meeting.

6.31 The submission described liraglutide as superior in terms of comparative effectiveness over exenatide, providing a statistically significant reduction in cardiovascular risk in patients with Type 2 diabetes and high cardiovascular risk. This claim was not adequately supported given the following:

- The single randomised controlled trial included in the submission compared liraglutide to placebo (with standard care) in the requested population and it was assumed that placebo was a reasonable proxy for exenatide in terms of cardiovascular outcomes. No clinical trial data for the cardiovascular outcomes of exenatide in the requested population were presented in the submission. The meta analyses referred to in the PSCR (pp.2-3) as showing no benefit for exenatide similarly showed no benefit for liraglutide; and
 - The comparative efficacy of liraglutide versus exenatide in combination therapy with insulin has not previously been considered by the PBAC and no clinical trial data relevant to this comparison was presented in the submission.
 - The ESC advised that liraglutide did demonstrate cardiovascular benefit and reduced death over placebo.
- 6.32 The submission described liraglutide as similar to exenatide in terms of comparative safety. This claim is not supported by comparative trial data for exenatide in the requested population. The claim of similar safety compared to exenatide was based on post marketing data in the broader Type 2 diabetes population. However, the PBAC has previously considered liraglutide 1.2 mg once daily to be non-inferior to exenatide 10 µg twice daily in terms of safety in dual and triple combination therapy (March 2013 liraglutide PSD, paragraph 12).
- 6.33 The PBAC considered that the claim superior comparative effectiveness of liraglutide 1.8mg daily for patients with T2DM at high cardiovascular risk compared with exenatide 10 µg twice daily was not reasonable due to a lack of supporting clinical evidence that excludes the cardiovascular effects of exenatide.
- 6.34 The PBAC recalled their previous recommendation from March 2013 and considered that the claim of non-inferior comparative safety was reasonable for liraglutide 1.2 mg once daily compared to exenatide 10 µg twice daily in terms of safety in dual and triple combination therapy.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.35 The submission presented a modelled cost utility analysis comparing the cardiovascular benefits of liraglutide with exenatide 10 µg twice daily.
- 6.36 Given the base case, which included the costs but not benefits of exenatide, is not informative and is biased in favour of liraglutide, the evaluation presented the results of the placebo comparison as the base case of the modelled economic evaluation. The ESC considered the base case modelled economic evaluation versus exenatide is only relevant if it is accepted that exenatide has no impact on CV events. The ESC noted that diabetes medications, including exenatide, have been recommended on the assumption of a reduction in final patient relevant outcomes including CV events. Therefore, the current price for exenatide incorporates the assumed benefit of a reduction in CV events. If it is claimed that exenatide has no

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impact on CV events it is inappropriate to use the current price of exenatide in the economic model. The ESC noted the ICER with the costs of exenatide removed was \$45,000/QALY – \$75,000/QALY. With the revised prices offered in the PSCR, the ICER is \$45,000/QALY – \$75,000/QALY. This ICER is relatively high and may suggest that the magnitude of the reduction in CV events observed with liraglutide in the LEADER trial does not support the requested price.

Table 10: Summary of model structure and rationale

Component	Summary
Methods used to generate results	Markov cohort model using cohort expected value analysis
Time horizon	10 years, with sensitivity analysis at 15 and 20 years
Cycle length	Monthly, no half cycle correction
Outcomes	Incremental cost per quality-adjusted life year (QALY) gained based on the primary and key secondary cardiovascular outcomes of the LEADER trial (cardiovascular death, nonfatal myocardial infarction, nephropathy)
Health states	Six health states: <ul style="list-style-type: none"> • Alive with no cardiovascular events; • Alive with myocardial infarction event; • Alive with nephropathy event; • Alive with both myocardial infarction and nephropathy events; • Dead from cardiovascular causes; and • Dead from non-cardiovascular causes
Transition/event probabilities	Transition probabilities were derived from the LEADER trial cardiovascular time-to-event outcomes (cardiovascular death, non-fatal myocardial infarction) and time to first nephropathy event as events per 100 patient years, converted to monthly probabilities Cardiovascular deaths: Liraglutide - 0.0010; placebo/exenatide - 0.0013 Non-fatal myocardial infarction: Liraglutide - 0.0016; placebo/exenatide - 0.0019 Nephropathy (renal failure): Liraglutide - 0.0013; placebo/exenatide - 0.0016 Severe hypoglycaemia event: Liraglutide/exenatide - 0.0008; placebo - 0.0013
Utilities	Baseline 0.800 (LEADER baseline EQ-5D) Myocardial infarction 0.745 (Afzali et al. 2013 and Clarke et al. 2002) Nephropathy 0.748 (Afzali et al. 2013 and Kiberd et al. 1995) Death 0
Discount rate	5% for costs and outcomes

Source: Constructed during the evaluation

6.37 Key issues with the economic model are summarised in the table below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Model structure	<p>The 10-year time horizon based on the mean age of participants in the LEADER trial assuming a shortened life expectancy in patients with Type 2 diabetes and high cardiovascular risk was not adequately justified.</p> <p>Inclusion of the "Alive with MI" health state may not have been appropriate, given the non-fatal myocardial infarction component of the primary composite outcome (MACE) in the LEADER trial demonstrated no statistically significant difference between liraglutide and placebo.</p>	<p>Unclear</p> <p>High, favours liraglutide</p>
Utilities	<p>The utility for nephropathy events was derived from a small time-trade-off study for insulin dependent diabetics in 17 health care workers in Canada in 1995, and may be unreliable.</p>	<p>High, favours liraglutide</p>
Healthcare costs	<p>The monthly cost of liraglutide (\$██████) was weighted across the requested prices of the two and three pen packs, using the ratio of exposure to liraglutide 1.8 mg:1.2 mg in the LEADER trial, and similarly adjusted by the mean dose of liraglutide used in LEADER. Using only the weighting method (applied to exenatide in the submission) the mean monthly cost of liraglutide increased to \$██████.</p> <p>The use of LEADER trial event rates for severe hypoglycaemia events may not be appropriate, given results for this outcome may have been skewed by an individual outlier in the placebo arm providing 61% of the difference between liraglutide and placebo.</p>	<p>High, favours liraglutide</p> <p>Moderate, favours liraglutide</p>

Source: Compiled during the evaluation

6.38 The results of the stepped economic evaluation for the comparison of liraglutide versus exenatide are summarised in Table 12.

Table 12: Results of the stepped economic evaluation: Liraglutide versus exenatide

Step - outcome	Incremental cost	Incremental outcome	ICER
Step 1: Trial based (54-month LEADER study data; drug costs only)			
- per cardiovascular event avoided	\$ [REDACTED]	-1.9%	\$ [REDACTED]
- per cardiovascular death avoided	\$ [REDACTED]	-1.3%	\$ [REDACTED]
- per myocardial event avoided	\$ [REDACTED]	-1.0%	\$ [REDACTED]
- per nephropathy event avoided	\$ [REDACTED]	-1.5%	\$ [REDACTED]
Step 2: Deaths (drug costs only, 10 years)			
- per death avoided	\$ [REDACTED]	-0.012	\$ [REDACTED]
Step 3: Discounted life years (drug costs only, 10 years)			
- per life year gained	\$ [REDACTED]	0.065	\$ [REDACTED]
Step 4: Discounted QALYs (drug costs only, 10 years)			
- per QALY gained	\$ [REDACTED]	0.058	\$ [REDACTED]
Step 5: Discounted QALYs (all costs, 10 years)			
- per QALY gained	\$ [REDACTED]	0.058	\$ [REDACTED]
Step 5 with revised prices from PSCR			
- per QALY gained	-\$ [REDACTED]	0.058	Liraglutide dominant
Step 5 with revised prices from PSCR (excluding non-fatal myocardial infarctions^a)			
- per QALY gained	-\$ [REDACTED]	0.055	Liraglutide dominant

Source: Table D.6.1, pp.163-164 of the submission; corrected for error in submission's table; values used as per spreadsheet.

Abbreviations: QALY, quality-adjusted life year

^a Non-fatal myocardial monthly probabilities for both treatment arms set to placebo probability of 0.0019 (i.e. no difference, placebo monthly probability)

- 6.39 The submission presented the comparison of liraglutide versus exenatide as the base case, which resulted in an incremental cost per QALY gained of less than \$15,000. This analysis was not informative, given the submission included the cost of exenatide, but assumed that exenatide would have no treatment effect in the modelled population.
- 6.40 The ESC noted the revised incremental cost effectiveness ratios in the PSCR (ICERs; Table 1) based on the new requested prices for liraglutide (liraglutide dominates placebo), and excluding the cost/utility impacts of non-fatal myocardial infarctions (not statistically significantly different from placebo in the LEADER trial; revised ICER less than \$15,000 per QALY). These revised ICERs could not be replicated. Use of a weighted cost of liraglutide across the 1.2 mg and 1.8 mg doses (2 and 3 pen packs) was inappropriate given the revised restriction applies only to the 1.8 mg once daily regimen (3 pen pack). However, using the revised prices in the PSCR, liraglutide is dominant in the base case cost effectiveness for liraglutide versus exenatide, both with and without the inclusion of non-fatal MIs.
- 6.41 The results of the stepped economic evaluation comparing liraglutide with placebo are summarised in Table 13.

Table 13: Results of the stepped economic evaluation: Liraglutide versus placebo

Step - outcome	Incremental cost	Incremental outcome	ICER
Step 1: Trial based (54-month LEADER study data; drug costs only)			
- per cardiovascular event avoided	\$ [REDACTED]	-1.9%	\$ [REDACTED]
- per cardiovascular death avoided	\$ [REDACTED]	-1.3%	\$ [REDACTED]
- per myocardial event avoided	\$ [REDACTED]	-1.0%	\$ [REDACTED]
- per nephropathy event avoided	\$ [REDACTED]	-1.5%	\$ [REDACTED]
Step 2: Deaths (drug costs only, 10 years)			
- per death avoided	\$ [REDACTED]	-0.012	\$ [REDACTED]
Step 3: Discounted life years (drug costs only, 10 years)			
- per life year gained	\$ [REDACTED]	0.065	\$ [REDACTED]
Step 4: Discounted QALYs (drug costs only, 10 years)			
- per QALY gained	\$ [REDACTED]	0.058	\$ [REDACTED]
Step 5: Discounted QALYs (all costs, 10 years)			
- per QALY gained	\$ [REDACTED]	0.058	\$ [REDACTED]
Step 5 with revised prices from PSCR			
- per QALY gained	\$ [REDACTED]	0.058	\$ [REDACTED]
Step 5 with revised prices from PSCR (excluding non-fatal myocardial infarctions^a)			
- per QALY gained	\$ [REDACTED]	0.055	\$ [REDACTED]

Source: Table D.6.1, pp.163-164 of the submission and additional calculations performed during the evaluation using 'Liraglutide_Section D model_final' spreadsheet provided with the submission.

^a Non-fatal myocardial monthly probabilities for both treatment arms set to placebo probability of 0.0019 (i.e. no difference, placebo monthly probability)

6.42 The incremental cost per QALY gained for liraglutide compared with placebo is \$45,000/QALY – \$75,000/QALY. Using the revised prices in the PSCR, the ICER comparing liraglutide with placebo is \$45,000/QALY – \$75,000/QALY.

6.43 Univariate sensitivity analysis presented in the submission around liraglutide dose and duration of therapy, time horizon, discount rate, patient baseline age, baseline utility, transition probabilities and cardiovascular medicines avoided, show little variation in the incremental cost effectiveness ratio. Univariate and multivariate sensitivity analysis conducted during the evaluation around the cost of liraglutide, the inclusion of non-fatal myocardial infarction as a health state and removal of avoided cardiovascular medicines showed high variability in the incremental cost effectiveness ratio, up to \$105,000/QALY – \$200,000/QALY gained.

Drug cost/patient/year: \$ [REDACTED]

6.44 Calculated during the evaluation (adjusted for reduced requested prices in PSCR) assuming 84.8% use of liraglutide 1.8 mg daily and 15.2% use of liraglutide 1.2 mg daily (LEADER Clinical Trial Report utilisation data) and [REDACTED] scripts per year excluding administration costs (i.e. $[[\$ [REDACTED] \times 0.848] + [\$ [REDACTED] \times [1-0.848]]] \times [365/30]$).

- 6.45 Using a similar approach for exenatide assuming 75.7% exenatide 10 µg and 24.3% 5 µg twice daily (PBS script volumes September 2015 to August 2016), the drug cost of exenatide was \$ [REDACTED] per patient per year. Using the weighted price of liraglutide applied in the submission (\$ [REDACTED]; see Table 11 above) the cost per patient per year for liraglutide was \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.46 This submission was considered by DUSC. The submission presented a mixed market share/epidemiological approach to estimate the extent of use and financial implication of listing liraglutide for the requested restriction. Exenatide once weekly has a Special Pricing Arrangement.
- 6.47 The submission used a complex multi-step approach to estimate the total number of patients in each market using a statistical software package (ForecastPro) and multiple sources of pack sales for liraglutide on the private market, and patient numbers from the PBS data.
- 6.48 The submission did not adequately justify the use of the complex, multi-step methods with multiple assumptions that required different datasets to estimate patient numbers in each market, given the sponsor had access to patient numbers from available datasets (e.g. Model Solutions PBS data). DUSC agreed with the commentary that the data sources and approach to financial estimates were unconventional. DUSC considered that the approach was not adequately justified and could have been strengthened by triangulating the estimates with the February 2017 DUSC diabetes analysis, which was provided to the sponsor prior to this submission.

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Table 14: Estimated use and financial implications of listing liraglutide for the requested restriction

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated liraglutide patients					
Total patients	██████	██████	██████	██████	██████
Estimated PBS-listed liraglutide scripts					
Total scripts (82% adherence; 12.17 per year) ^a	██████	██████	██████	██████	██████
- 3 pen pack (42%)	██████	██████	██████	██████	██████
- 2 pen pack (58%)	██████	██████	██████	██████	██████
Total cost to PBS (DPMQ)	\$██████	\$██████	\$██████	\$██████	\$██████
- 3 pen pack (\$██████)	\$██████	\$██████	\$██████	\$██████	\$██████
- 2 pen pack (\$██████)	\$██████	\$██████	\$██████	\$██████	\$██████
Total co-payments	\$██████	\$██████	\$██████	\$██████	\$██████
Total PBS/RPBS cost less co-payments	\$██████	\$██████	\$██████	\$██████	\$██████
Cost offsets (drug costs based on published DPMQ less patient co-payment)					
Exenatide substitution ^b	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
DPP4 and DPP4/MET substitution ^c	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
SGLT2 and SGLT2/MET substitution	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Exenatide twice daily needles (\$██████) ^d	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Exenatide once weekly needles (\$██████) ^d	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Increased costs (drug costs based on DPMQ less patient co-payment)					
Metformin (single ingredient products) ^e	\$██████	\$██████	\$██████	\$██████	\$██████
Liraglutide needles (\$██████) ^d	\$██████	\$██████	\$██████	\$██████	\$██████
Total costs					
Net cost to PBS/RPBS less co-payments	\$██████	\$██████	\$██████	\$██████	\$██████
Net cost to government	\$██████	\$██████	\$██████	\$██████	\$██████

Source: 'Liraglutide_Section E model_final' Excel workbook in the submission

Abbreviations: DPMQ, dispensed price maximum quantity; DPP4, dipeptidyl peptidase-4; MET, metformin; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SGLT2, sodium glucose co-transporter 2

^a The submission made a calculation error when making an adjustment to account for patients initiating treatment throughout the year (half-cycle correction) resulting in half the expected utilisation in Year 1 and a further 4 full years of listing (Year 2-5).

^b Based on published DPMQ \$130.38. Exenatide once weekly is subject to Special Pricing Arrangement.

^c Estimates in the submission were calculated using published DPMQ as of 1 February 2017. The published DPMQ as of 1 May 2017 for linagliptin and saxagliptin products were slightly lower due to price reductions. Estimates were not corrected during evaluation.

^d Needle cost per script calculated based on number of doses administered per script assuming 12.2 scripts per year and 82% adherence.

^e The submission made an error and omitted increased costs associated with SGLT2/MET FDC substitution. The error was not corrected during evaluation as the budget impact was minor.

6.49 The proposed listing of liraglutide on the PBS/RPBS for patients with type 2 diabetes at high risk of cardiovascular disease was estimated to cost \$30 – \$60 million in the fifth year of listing. The estimated cumulative cost to the PBS/RPBS over five years was more than \$100 million. Note, the estimates reflect the original submission financial implications as the revised estimates from the PSCR including the lower price offer could not replicated.

- 6.50 The proposed listing was associated with substantial cost-offsets primarily due to substitution of other glucose-lowering drugs (exenatide, DPP4 inhibitor and DPP4/metformin FDC, SGLT2 inhibitor and SGLT2/metformin FDC). There were also increased costs associated with increased metformin (single ingredient products) utilisation due to liraglutide substitution of FDCs as well as increased needle use for liraglutide administration due to substitution of oral drugs with an injectable.
- 6.51 The submission assumed that liraglutide will not grow the overall market and did not consider other treatments identified in the treatment algorithm with the potential for substitution such as insulin, thiazolidinediones or sulfonylureas. DUSC considered that the submission should have included potential substitution from other diabetes therapies; particularly insulin and possibly sulfonylureas.
- 6.52 The submission inappropriately applied half-cycle correction to utilisation estimates for liraglutide.
- 6.53 The estimated proportion of patients with type 2 diabetes at high risk of cardiovascular events (68.5%) was based on Australian adults above 18 years of age with cardiovascular disease or nephropathy (AIHW Cardiovascular Disease, Diabetes and Chronic Kidney Disease Report 2015). The proportion is inconsistent with the requested restriction (aged over 50 years) and is likely to be an underestimate as it does not consider increasing cardiovascular risk with age or smoking status (National Stroke Foundation 2012).
- 6.54 At year 5, the estimated number of patients was 50,000 – 100,000 and the net cost to the PBS would be \$30 – \$60 million. DUSC considered it is unlikely the market for liraglutide would be as large as predicted in Year 5. The forecasting method overestimates all markets that liraglutide may substitute in the outer years, the estimate is much higher than the extent of use of exenatide, and a recent study of empagliflozin that reported a reduction in deaths from CV causes may impact on uptake of liraglutide.
- 6.55 DUSC considered the number of patients taking exenatide, DPP-4 inhibitors or SGLT2 inhibitors was overestimated by the submission due to the data source (IMS) containing non-PBS use.
- 6.56 DUSC considered it was unreasonable to assume that all patients on non-PBS liraglutide would switch to PBS-subsidised liraglutide if it were listed. DUSC considered it likely that many users of non-PBS-subsidised liraglutide would not meet the requested restriction and some may be prescribed liraglutide for an indication other than T2DM (e.g. weight loss). Additionally, as the disease characteristics of the patients on non-PBS liraglutide are unclear, it is uncertain that 68.5% of them would meet the requested restriction criteria.
- 6.57 The submission assumed different uptake rates (from incident and prevalent populations) for each treatment except for the SGLT2 inhibitor market where uptake and switch rates were assumed to be the same. The submission did not justify the

differences in the magnitude of the uptake rates that ranged between 2% and 80%. Using the assumed rates, DPP-4 inhibitors followed by SGLT2 inhibitors have the largest number of patients with treatments substituted with liraglutide. DUSC reiterated that no basis was provided for the liraglutide uptake rates and thus it considered the uptake rates to be uncertain.

Quality Use of Medicines

- 6.46 The sponsor proposed providing educational and promotional activities aimed at minimising use of liraglutide outside the requested restriction

Financial Management – Risk Sharing Arrangements

- 6.47 The sponsor proposed a risk share arrangement to offset uncertainty in the economic model, based on a revenue/utilisation cap.

For more detail on PBAC's view, see section 7 "PBAC outcome."

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of liraglutide 1.8 mg daily for treatment of patients with Type 2 diabetes mellitus and high cardiovascular risk on the basis of inadequate comparative clinical data and uncertain cost effectiveness.
- 7.2 The PBAC reaffirmed its March 2013 recommendation to list liraglutide 1.2 mg once daily on a cost minimisation basis with exenatide 10 µg twice daily for dual combination therapy with metformin or a sulfonylurea, and as triple combination therapy with metformin and a sulfonylurea. The PBAC noted this recommendation did not include combination use with insulin. The PBAC also noted the recommendation for the 1.2 mg liraglutide dose from March 2013 is due to be revoked in March 2018 and in reaffirming its recommendation extended it until July 2022.
- 7.3 The PBAC considered the proposed restriction for the 1.8 mg dose is complex and may exclude patients who would benefit from liraglutide. Whilst the criteria for high cardiovascular risk in the restriction are consistent with the inclusion criteria of the LEADER trial they are not consistent with Australian best practice guidelines, and are unlikely to be used in clinical practice. Furthermore, the criteria for patients ≥60 years with microalbuminuria or proteinuria appeared to be contrary to the pre-specified subgroup analysis in the LEADER trial for patients >60 years of age and at high CV risk, with the major adverse cardiovascular event (MACE) outcome favouring placebo (although the difference was not statistically significant (HR 1.20, 95% CI [0.86-1.67], but with a positive test for interaction). The PBAC also agreed with ESC that implementing the different restrictions associated with the 1.2 mg and 1.8 mg doses would not be workable in clinical practice given the overlapping eligibility of the patient groups.

- 7.4 The PBAC accepted exenatide (PBS listed GLP-1 agonist) was an appropriate comparator. The PBAC agreed with ESC that empagliflozin may also be replaced in clinical practice and is also a relevant comparator. Although a different mode of administration (oral as opposed to injectable) and different mechanism of action, SGLT-2 inhibitors have established a class effect in reducing CV outcomes and prescribing may target the same patient group proposed for 1.8 mg liraglutide. The PBAC noted that despite not having a specific PBS listing for high CV risk patients, empagliflozin offers similar reductions in direct CV outcomes across the broader Type 2 diabetes population at a substantially lower price. Based on results of the EMPA-REG OUTCOME trial, empagliflozin offers a statistically significant improvement compared to placebo for the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR 0.86, 95% CI [0.74, 0.99])
- 7.5 The PBAC accepted the evidence presented from the LEADER trial showed liraglutide had a reduction in MACE outcomes compared with placebo; a 13.2% reduction in risk of a MACE compared to placebo (HR 0.87, 95% CI [0.78, 0.97]). However, the PBAC was not satisfied that liraglutide showed superior comparative effectiveness over exenatide based on the submission's assumption that the placebo arm of the LEADER trial was reasonable proxy for exenatide.
- 7.6 The PBAC was not satisfied that liraglutide has a unique effect on cardiovascular outcomes. The PBAC discussed how increased regulatory scrutiny on the cardiovascular safety of new diabetes medications has led to increased assessment of these therapies. The PBAC referenced the SUSTAIN-6 trial², a randomised trial that compared semaglutide with placebo in patients with T2DM who were at high cardiovascular risk. The study demonstrated a lower risk of cardiovascular outcomes in patients receiving semaglutide compared with placebo (statistically significant improvement for the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; HR 0.74, 95% CI [0.58, 0.95]). The PBAC considered in the absence of clinical trial data that demonstrates exenatide has no cardiovascular effect, it is likely there is a class effect across the GLP-1 analogues.
- 7.7 The PBAC noted results of the exenatide EXSCEL cardiovascular outcomes trial are expected to be presented at the European Association for the Study of Diabetes (EASD) annual meeting in September 2017. The PBAC noted the exenatide EXSCEL cardiovascular outcomes trial press release stated that although statistical significance was not reached, there were fewer CV events observed with exenatide. The PBAC considered an indirect comparison of liraglutide and exenatide including full evaluation of the EXSCEL trial patient characteristics and trial results was required to quantify how the CV benefits of liraglutide compare to exenatide.

² Marso SP, Bain SC, Consoli A, 2016, 'Semaglutide and cardiovascular outcomes in patients with type 2 diabetes', *New England Journal of Medicine*; 375(19): 1834-1844.

- 7.8 The PBAC recalled it has previously considered liraglutide 1.2 mg once daily to be non-inferior to exenatide 10 µg twice daily in terms of safety when used as dual combination therapy with metformin or a sulfonylurea, and as triple combination therapy with metformin and a sulfonylurea (March 2013 liraglutide PSD, paragraph 12). It also noted the reported adverse events in the LEADER trial were consistent with those reported in the broader populations previously considered by the PBAC (liraglutide PSD November 2010, November 2011 and March 2013). However, the proportions of patients reporting all events were substantially smaller in the LEADER trial. Therefore, overall the PBAC did not have specific safety concerns.
- 7.9 The PBAC considered that the base case economic model did not provide a reliable indication of the cost effectiveness of liraglutide versus exenatide in terms of cardiovascular risk. It noted the economic evaluation assumed that exenatide has no impact of cardiovascular outcomes; however, this claim was not supported by the evidence in the submission. Further, the PBAC agreed with the ESC that PBS subsidised diabetes medications have been recommended on the basis of an assumed reduction in CV events and the current price of diabetes medications, including exenatide, incorporates this assumed benefit. If it is claimed that exenatide has no impact on CV events it is inappropriate to use the current price of exenatide in the economic model. The ESC noted the ICER with the costs of exenatide removed was \$45,000/QALY – \$75,000/QALY. With the revised prices offered in the PSCR the ICER is \$45,000/QALY – \$75,000/QALY. The PBAC noted this ICER is relatively high and suggests that the magnitude of the reduction in CV events observed with liraglutide in the LEADER trial may not support the requested price.
- 7.10 The PBAC noted the advice from DUSC and agreed that the estimates of patients likely to use liraglutide were highly uncertain. The PBAC agreed that along with other utilisation issues, the requested restriction criteria would likely exclude patients currently receiving non-PBS liraglutide. In addition it was not reasonable to assume liraglutide will not replace other PBS medications already in use in the high cardiovascular risk population and there is a high risk of potential use outside the proposed restriction.
- 7.11 The PBAC considered a major resubmission would be most informative if it included:
- December ACM meeting advice for review of the proposed indication
 - results from the EXSCEL trial (for consideration of exenatide as the main comparator)
 - consideration of liraglutide in the broader context of other glucose lowering comparators likely to be replaced, such as empagliflozin
 - consideration of the additive benefit of liraglutide compared with other CV lowering therapies (lifestyle, blood pressure lowering, statins, antithrombotics, ACEi/ARBs)

- clarification of the restriction criteria to identify those in the Australian population most likely to benefit, in the context of the subgroup analysis from the relevant trial
- an economic evaluation that includes:
 - reduction in cardiovascular risk likely from comparators or more complete justification why no CV benefit is assumed
 - only health states for which liraglutide has demonstrable incremental benefit.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.

ⁱ N Engl J Med 2016; 375:311-322 [July 28, 2016](#) DOI: 10.1056/NEJMoa1603827