5.10 SEMAGLUTIDE, Injection 2 mg in 1.5 mL pre-filled syringe and Injection 4 mg in 3 mL pre-filled syringe, Ozempic®, Novo Nordisk Pharmaceuticals Pty Ltd

1 Purpose of Application

1.1 The submission requested a Section 85, Streamlined Authority listing for semaglutide (injectable) for treatment of patients with type 2 diabetes who have inadequate glycaemic control, as dual therapy in combination with metformin or a sulfonylurea where either of these is contraindicated or not tolerated; or triple therapy in combination with metformin and a sulfonylurea. The PBAC has not previously considered semaglutide (injectable).

1.2 Listing was requested on a cost-effectiveness basis for high dose semaglutide compared to exenatide once weekly. The cost-effectiveness of low dose and high dose semaglutide compared to dulaglutide once weekly was also presented as a supportive analysis.

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

Component	Description
Population	Adult patients with type 2 diabetes mellitus who have inadequate glycaemic control with metformin and a sulfonylurea, or with metformin or a sulfonylurea where either of these is contraindicated/not tolerated
Intervention	Semaglutide 0.25 mg SC injection once weekly for 4 weeks increasing to 0.5 mg once weekly for 4 weeks, with potential up-titration to 1 mg once weekly if required
Comparator	Main: Exenatide 2.0 mg SC injection once weekly Secondary: Dulaglutide 1.5 mg SC injection once weekly
Outcomes	Improved glycaemic control and body weight management. These changes may also lead to reduced macrovascular and microvascular complications, and morbidity and mortality associated with these complications
Clinical claim	Semaglutide 1.0 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety compared with exenatide 2.0 mg once weekly, when used in dual or triple therapy. Semaglutide 0.5 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety compared with dulaglutide 1.5 mg once weekly, when used in dual therapy. Semaglutide 1.0 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety compared with dulaglutide 1.5 mg once weekly, when used in dual therapy.

Source: Table 1-1, p 30 of the submission
Abbreviation: SC, subcutaneous

2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SEMAGLUTIDE				Ozempic® Novo Nordisk
1.34 mg/1 mL injection, 1.5 mL pen device	1	5	$[redacted] (Published)	
1.34 mg/1 mL injection, 3 mL pen device	1	5	$[redacted] (Published)	Ozempic® Novo Nordisk

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	~~Chronic~~
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	~~Initial and continuing~~
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea, AND Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR Patient must not have tolerated a combination of metformin and a sulfonylurea, AND Patient must have, or have had, a 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 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.
Definitions:	~~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. 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.~~ ~~Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:~~ ~~(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or~~ ~~(b) Had red cell transfusion within the previous 3 months.~~ ~~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.~~

Prescriber Instructions:	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. 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.
Administrative Advice:	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor. Special Pricing Arrangements Apply [TBC]

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	~~Chronic~~
Severity:	~~NA~~
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Treatment phase:	~~Initial and continuing~~
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	The treatment must be in combination with metformin, AND The treatment must be in combination with a sulfonylurea, AND Patient must have, or have had, a 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 maximally tolerated doses of metformin and a sulfonylurea; OR 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 maximally tolerated doses of metformin and a sulfonylurea.

Definitions:	~~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. 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.~~ ~~Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:~~ ~~(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or~~ ~~(b) Had red cell transfusion within the previous 3 months.~~ ~~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.~~
Prescriber Instructions:	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. 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.
Administrative Advice:	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor. Special Pricing Arrangements Apply [TBC]

2.2 The recommended titration regimen for semaglutide involves a starting dose of 0.25 mg once weekly, increasing to 0.5 mg once weekly after 4 weeks, then increasing again to a maximum of 1 mg once weekly after 4 weeks if required to further improve glycaemic control. The 0.25 mg dose is not considered suitable for maintenance therapy. The 2.0 mg in 1.5 mL pre-filled multi-dose pen is intended for both initiation and maintenance therapy whereas the 4.0 mg in 3 mL is intended for maintenance therapy at the higher dose.

2.3 The submission proposed the same price for both presentations of semaglutide claiming the same approach applied to other PBS-listed type 2 diabetes medicines including empagliflozin and sitagliptin. There was no formal comparison of efficacy and safety between the two doses. Although the magnitude of difference between the doses remains unclear, the relative changes in HbA1c and weight loss are likely to be lower with low dose semaglutide (0.5 mg once weekly) than with high dose semaglutide (1.0 mg once weekly). The PBAC noted that the effects of semaglutide are

attenuated if not titrated to the maximum dose (1.0 mg) (see Tables 6 and 7 in the Comparative effectiveness section below).

2.4 The submission also claimed that there would be limited use of low-dose semaglutide 0.5 mg once weekly in practice. There was no justification provided for this assumption. Given the relatively high response rates to HbA1c and weight loss targets observed with low dose semaglutide and poorer tolerability profile associated with high dose semaglutide, it is probable that a substantial number of patients will use low dose semaglutide as maintenance therapy.

2.5 The Pre-Sub-Committee Response (PSCR) maintained that the majority of patients on semaglutide will titrate to the high dose (1.0 mg), therefore, results from the high dose comparison of semaglutide 1.0 mg versus dulaglutide 1.5 mg would be generalisable to the PBS population. The Economics Sub-Committee (ESC) noted there were no data presented in support of this assumption. In practice, the titration of semaglutide is likely to be more flexible (e.g. also allowing for down-titration), dependent on HbA1c response, weight loss response and tolerability; which is different to the fixed doses administered in the trials. The ESC considered that higher incidence of gastrointestinal side effects may result in increased use of lower dose semaglutide, which is likely to be associated with reduced benefits in HbA1c control and weight reduction. The Pre-PBAC Response accepted that the comparative clinical and cost effectiveness of the 0.5mg semaglutide dose is likely to be considered non-inferior to dulaglutide and exenatide and that a cost-minimisation analysis would be appropriate.

2.6 The requested restriction was identical to the PBS restriction for exenatide once weekly, allowing for use with metformin and/or sulfonylurea. The requested restriction was narrower than the proposed TGA indication that includes use as monotherapy in patients who are intolerant/contraindicated to metformin and use in combination with any other medicines for the treatment of type 2 diabetes.

2.7 There was potential risk of use outside of the proposed restriction as there are differences between GLP-1 therapies currently available on the PBS (only exenatide twice daily can be used with insulin) which may lead to prescriber confusion. There is a request for an extension of listing for dulaglutide for use with insulin, which will be considered during the November 2019 PBAC meeting. A trial of semaglutide used as an add-on to basal insulin is complete (SUSTAIN 5, Rodbard 2018) and a trial of semaglutide versus insulin aspart when used in combination with metformin and insulin glargine is underway (SUSTAIN 11, expected completion in 2021). The ESC also noted potential use in combination with SGLT2-inhibitors, citing the TGA Delegate's file note from 2 August 2019, which stated that: "[redacted]." (TGA Delegate file note, 2 August 2019). Additionally, ADA and EASD guidelines suggest the use of GLP-1 therapies in combination with SGLT2-inhibitor therapies.

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

3 Background

Registration status

3.1 Semaglutide (injectable) was submitted under the TGA/PBAC parallel process. Semaglutide (injectable) was TGA registered on 28 August 2019 for treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- As monotherapy when metformin is not tolerated or contraindicated
- In addition to other medicinal products for the treatment of type 2 diabetes mellitus

3.2 The draft product information and First Round TGA Clinical Evaluator's Report were provided with the submission and available during the evaluation. No other TGA documents were available. The TGA delegate's decision was received on 19 August 2019.

[redacted]

4 Population and disease

4.1 Type 2 diabetes mellitus is the most common type of diabetes in adults and is characterised by hyperglycaemia associated with variable degrees of impaired insulin secretion and peripheral resistance to insulin. It is a chronic condition associated with a range of hereditary and lifestyle risk factors including poor diet, insufficient physical activity and being overweight or obese. Overall disease prevalence in Australia is increasing over time but it is more common in men, the elderly, Aboriginal and Torres Strait Islanders and socially disadvantaged populations.

4.2 Diabetes complications are divided into microvascular (damage to small blood vessels) and macrovascular (damage to large blood vessels). Microvascular complications include damage to eyes (retinopathy) leading to blindness, to kidneys (nephropathy) leading to renal failure, to nerves (neuropathy) and diabetic foot disorders (which include severe infections leading to amputation). Macrovascular complications include cardiovascular diseases such as myocardial infarction, stroke and peripheral vascular disease.

4.3 The proposed algorithm positions semaglutide as an alternative to existing GLP-1 analogues for use as dual therapy in combination with metformin or sulfonylurea where either treatment is contraindicated or not tolerated; or in triple therapy in combination with metformin and sulfonylurea. This was broadly consistent with current PBS listings of GLP-1 analogues, which is the same as for exenatide once weekly but narrower than exenatide twice daily (can be used in combination with insulin) and broader than dulaglutide (dual therapy is with metformin only).

The clinical place in therapy of GLP-1 therapies is still being established, with utilisation data suggesting rapid market expansion primarily driven by the uptake of dulaglutide. Recently published international guidelines suggest earlier use of GLP-1 analogues (or SGLT2 inhibitors) due to cardiovascular benefits, lower risk of hypoglycaemia and weight loss benefits (ADA-EASD 2018 Consensus Report[1]). These guidelines recommend that the choice of glucose-lowering medications added to metformin should be based on patient comorbidities (such as the presence of cardiovascular disease, heart failure and kidney disease) and individual concerns (such as, hypoglycaemic risk, minimising weight gain/promoting weight loss, safety, tolerability, and cost). Updated Australian guidelines for the management of type 2 diabetes are expected to be published by the Australian Diabetes Society (ADS) and the Royal Australian College of General Practitioners (RACGP) in 2020.

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

5 Comparator

5.1 The submission nominated exenatide once weekly as a main comparator. Exenatide once weekly is a pharmacological analogue to semaglutide (also a GLP-1 analogue) with the same method and frequency of administration, although it does not require dose titration. It is currently listed on the PBS for use in dual and triple combination therapy with metformin and/or sulfonylurea. The nominated comparator was appropriate.

5.2 The submission nominated dulaglutide once weekly as a secondary comparator. Within the GLP-1 market, the submission argued that exenatide once weekly would be the therapy most likely to be replaced as it currently has the largest market share based on PBS utilisation data. However, the submission acknowledged that dulaglutide was only recently listed (June 2018) and has rapidly accrued a majority share of new GLP-1 initiations. The ESC considered that dulaglutide was a relevant comparator given similarities between treatment regimens, overlapping indications and the rapid rise in market share compared to other GLP-1 therapies. Based on the

[1] Davies, M.J., D'Alessio, D.A., Fradkin, J. et al.
Jointly published in: Diabetes Care 2018 Dec; 41(12): 2669-2701; and Diabetologia 2018 Dec; 61(12): 2461 - 2498

PBAC recommendation for dulaglutide (cost-minimised against exenatide once weekly and twice daily), its price would be lower than that of exenatide once weekly (para 7.2, dulaglutide Public Summary Document (PSD) Nov 2017; para 7.1 exenatide PSD July 2015). In the context of the cost-utility approach taken by the submission, a further consideration for PBAC was that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy.

5.3 The submission claimed that semaglutide may also substitute for other therapeutic classes of anti-diabetic medicines including DPP4 inhibitors, SGLT2 inhibitors, sulfonylureas, thiazolidinediones, and insulin. The sponsor further anticipated that the improved efficacy associated with semaglutide may lead to an expansion of the clinical place of GLP-1 treatments to gradually replace oral therapies. Based on PBS utilisation data, it is likely that DPP4 inhibitors, SGLT2 inhibitors, sulfonylureas and insulin are relevant comparators given their substantial market size alongside the rapidly growing market share of GLP-1 therapies.

5.4 The submission claimed that there are no near market comparators but noted the pending availability of oral semaglutide. The clinical trial program consists of 10 Phase 3 trials (PIONEER 1-10) which are now complete, several of which have published results. Marketing authorisation has been granted in the US (FDA approval as of 20 September 2019) and at the time of the PBAC meeting it was under review by several regulatory agencies including the EMA and the Japanese Pharmaceuticals and Medical Devices Agency. Oral semaglutide was considered a near market entrant that is likely to shift the clinical place in therapy of semaglutide to directly compete with other oral agents.

5.5 The PSCR claimed that the availability of oral semaglutide should not impact the consideration of injectable semaglutide as the sponsor considered these presentations to be fundamentally different therapies in terms of method of administration, dosing, efficacy and safety profiles, and likely place in therapy. The PSCR also noted that [redacted] The ESC agreed with the evaluation that the potential future entry to the Australian market of oral semaglutide was relevant in consideration of the disruption to the market and treatment algorithm for all injectable therapies for type 2 diabetes.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (6) and organisations (1) via the Consumer Comments facility on the PBS website. The comments were all positive and described a range of benefits of treatment with semaglutide including the superior clinical effects on glycaemic control, weight loss and cardiovascular protection versus comparators, weekly dosing aiding with compliance, and positive effects on morbidity, mortality and quality of life. The PBAC noted the superiority claim was not adequately supported by the clinical trial data.

6.3 The PBAC noted previous correspondence from the Australian Diabetes Society:

In light of recent evidence, and in keeping with a number of major guidelines around the world, we would consider that evidence for the addition of SGLT2 inhibitors or GLP1 analogues is strong for people meeting all of the following broad criteria:

- Type 2 diabetes
- Established cardiovascular disease or the presence of multiple cardiovascular risk factors
- HbA1c >6.5%.

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

Clinical trials

6.4 The submission was based on the following comparisons:

- Direct comparison of semaglutide 1.0 mg once weekly and exenatide 2.0 mg once weekly (SUSTAIN 3).
- Direct comparison of semaglutide 0.5 mg once weekly and semaglutide 1.0 mg once weekly with dulaglutide 1.5 mg once weekly (SUSTAIN 7).
- The PSCR provided results from a post-hoc analysis comparing 0.5 mg semaglutide once weekly and 1.5 mg dulaglutide once weekly (SUSTAIN 7).
- Supportive cardiovascular safety and long-term outcomes data of semaglutide 0.5 mg once weekly and semaglutide 1.0 mg once weekly versus placebo (SUSTAIN 6).

6.5 No trials were identified that provided direct comparative evidence of the following: semaglutide 0.5 mg once weekly versus exenatide 2.0 mg once weekly in dual or triple therapy with metformin and/or sulfonylurea; and semaglutide 0.5 mg or 1.0 mg once weekly versus dulaglutide 1.5 mg in triple therapy with metformin and sulfonylurea. There were limited data for semaglutide as dual therapy with sulfonylurea.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SUSTAIN 3 (NCT01885208)	Novo Nordisk Clinical Trial Report (2016). Efficacy and safety of semaglutide once-weekly versus exenatide ER 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs (OADs) in subjects with type 2 diabetes	Internal study report
	Ahmann AJ, Capehorn M, Charpentier G et al (2018). Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial	Diabetes Care;41(2):258-266
SUSTAIN 7 (NCT02648204)	Novo Nordisk Clinical Trial Report (2017). Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes	Internal study report
	Pratley RE, Aroda VR, Lingvay I et al (2018). Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial	Lancet Diabetes & Endocrinology;6(4):275-86
SUSTAIN 6 (NCT01720446)	Novo Nordisk Clinical Trial Report (2016). A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes	Internal study report
	Marso SP, Bain SC, Consoli A et al (2016). Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes	New England Journal of Medicine;375(19):1834-1844

Source: Table 2-4, p 54 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
SUSTAIN 3	809	R, MC, OL, PG 56 weeks	High	Type 2 diabetes on metformin alone and/or TZD or SU	Change in HbA1c and body weight	Change in HbA1c, BMI and other biomarkers
SUSTAIN 7	1,199	R, MC, OL, PG 40 weeks	High	Type 2 diabetes on metformin alone	Change in HbA1c and body weight	Change in HbA1c, BMI and other biomarkers
SUSTAIN 6	3,297	R, MC, DB, PG 104 weeks	Low	Type 2 diabetes, ≥ 50 years who are treatment-naïve or on up to 2 oral anti-diabetics, with or without insulin; and have high CV risk	Cardiovascular events, microvascular complications, change in HbA1c and body weight	Not used

Source: Section 2.3 and 2.4, pp 58-81 of the submission

Abbreviations: CV, cardiovascular; DB, double-blind, MC, multi-centre; OL, open-label; PG, parallel-group; R, randomised; SU, sulfonylurea; TZD, thiazolidinediones

6.8 The open-label trial design for the SUSTAIN 3 and SUSTAIN 7 trials had the potential to introduce bias as knowledge of treatment assignment may affect disease management decisions (particularly the use of concomitant medications), patient expectations and adherence.

6.9 There was differential discontinuation between treatment arms observed in SUSTAIN 7 and SUSTAIN 6 trials, primarily due to higher rates of gastrointestinal adverse events in the semaglutide treatment arms. Although overall discontinuation rates were

similar between arms in the SUSTAIN 3 trial, more patients in the semaglutide treatment arm discontinued due to gastrointestinal adverse events compared with the exenatide arm. The impact of these differences on outcomes in the trials was unclear.

Comparative effectiveness

6.10 The key trials used subsets of the full analysis set, labelled as 'on-treatment without rescue medication' when reporting the primary outcome of change in HbA1c and secondary outcome of change in body weight. The observation period for this dataset censored for premature treatment discontinuations as well as use of anti-diabetic rescue medications. Results from pre-specified sensitivity analyses using alternative datasets including an in-trial analysis (larger set including observations from patients who discontinued treatment prematurely) were consistent with the primary analysis in terms of statistical significance, although there were numerical differences between the point estimates which appeared less favourable for semaglutide versus the comparator arms.

6.11 The submission noted there is no consensus between decision makers (regulatory, reimbursement or guidelines) in terms of a minimal clinically important difference (MCID) for individual outcomes based on HbA1c and body weight. The submission nominated MCIDs as statistically significant differences of > 0.3% change from baseline HbA1c, > 3.0% change from baseline body weight, > 20% more patients achieving either HbA1c < 7.0% or ≤ 6.5%; and > 20 % more patients achieving a 5% reduction in body weight. The PBAC has previously accepted HbA1c differences of 0.3-0.4% as a non-inferiority margin in the context of non-inferiority claims but has not accepted an MCID for superiority claims. The ESC noted that there is no defined cut-off for determining superiority, however in clinical practice a reduction of 0.5% in HbA1c is used to assess treatment efficacy, in both the Australian Diabetes Society (ADS) Australian blood glucose treatment algorithm[2] and in primary care trials.

6.12 The submission claimed that there are limited data in support of an MCID for weight loss in type 2 diabetes. Regulatory guidelines for weight management products suggest efficacy benchmarks after 1 year of treatment of either: statistically significant difference in weight loss of ≥ 5% between arms; or the proportion of patients with ≥ 5% weight loss is at least 35% in the intervention arm, is approximately double the proportion in the placebo arm, and the difference between arms is statistically significant (FDA Draft Guidance Feb 2007). The PBAC has not previously accepted a superiority claim for weight loss in type 2 diabetes patients due to limitations in the body of evidence provided, with particular concerns regarding long term benefits and durability of weight loss associated with exenatide (exenatide PSD Nov 2008). The PBAC had also previously raised concerns regarding nominated targets for clinically

[2] http://t2d.diabetessociety.com.au/documents/vNuZ2sHG.pdf

meaningful weight loss in the absence of data surrounding long-term cardiovascular benefits (sibutramine Nov 2006 PSD). The ESC considered a 3 kg weight loss may be considered important in clinical practice, however it was unclear what the long-term impact of this weight change would be, particularly when treatment was stopped/switched.

6.13 The clinical importance of the combined MCID for both HbA1c and weight loss effects nominated in the submission remains unclear.

SUSTAIN 3 (semaglutide 1.0 mg versus exenatide 2.0 mg in dual or triple therapy with metformin and/or sulfonylurea)

6.14 Key outcomes for change in HbA1c from the SUSTAIN 3 trial are presented in the table below.

Table 4: Change in HbA1c (%) and proportion of patients achieving an HbA1c target of < 7.0% from baseline to week 56 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 56, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference (95% CI)[a]
Change in HbA1c (%) from baseline to week 56 [primary outcome]					
Sema 1.0 mg	291	8.36 (0.95)	6.81 (0.06)	-1.54 (0.06)	-0.62 (-0.80, -0.44)
Exenatide 2.0 mg	271	8.33 (0.96)	7.43 (0.06)	-0.92 (0.06)	
Treatment arms	**N**	**Patients, n/N (%)**			**Odds ratio (95% CI)**
Proportion of subjects achieving an HbA1c target of < 7.0% at week 56 [exploratory outcome]					
Sema 1.0 mg	404	270/404 (67)			3.88 (2.80, 5.38)
Exenatide 2.0 mg	405	161/405 (40)			

Source: Table 14.2.2, p 737 of the SUSTAIN 3 trial report; Table 11-3, p 159 of the SUSTAIN 3 trial report
Abbreviation: CI, confidence interval; SD, standard deviation; SE, standard error; sema, semaglutide
[a] Estimated using a mixed model for repeated measures (treatment and country as fixed factors and baseline value as covariate)

6.15 Treatment with semaglutide 1.0 mg once weekly was associated with a statistically significant reduction in percentage HbA1c from baseline to week 56 compared with exenatide 2.0 mg once weekly. At week 56, statistically significantly more patients achieved an HbA1c < 7.0% with semaglutide 1.0 mg once weekly compared with exenatide 2.0 mg once weekly. These results should be interpreted with caution due to the open-label trial design. In addition, the authors of the trial publication note the use of a vial and syringe for the administration of exenatide in the trial (instead of pre-filled pens) which may have affected treatment compliance (Ahmann et al 2018). The ESC considered the exenatide vial and syringe administration could have led to bias in the study outcomes with increased discontinuations and/or lower adherence compared to the devices that are now available.

6.16 The results met the glycaemic control component of the MCID for superiority nominated in the submission based on percentage HbA1c of more than 0.3% and at least 20% more patients achieving an HbA1c of < 7.0%. The ESC noted that the mean treatment difference also met the clinically significant 0.5% change in accordance with the ADS treatment algorithm.

6.17 Results for change in body weight from the SUSTAIN 3 trial are summarised in the table below.

Table 5: Change in body weight and the proportion of patients achieving ≥ 5% weight loss from baseline to week 56 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 56, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference (95% CI)[a]
Body weight (kg) [secondary endpoint]					
Sema 1.0 mg	295	96.21 (22.5)	91.23 (0.29)	-5.63 (0.29)	-3.78 (-4.58, -2.98)
Exenatide 2.0 mg	276	95.37 (20.5)	93.93 (0.29)	-1.85 (0.29)	
Body weight (%) [exploratory endpoint]					
Sema 1.0 mg	295	-	-	-5.98 (0.29)	-4.19 (-5.02, -3.36)
Exenatide 2.0 mg	276	-	-	-1.79 (0.30)	
Treatment arms	**N**	**Patients, n/N (%)**			**Odds ratio (95% CI)**
Proportion of subjects achieving ≥ 5% weight loss at 56 weeks [exploratory outcome]					
Sema 1.0 mg	404	212/404 (52)			5.12 (3.68, 7.11)
Exenatide 2.0 mg	405	70/405 (17)			

Source: Table 14.2.145, p 908; Table 14.2.143, p 904; Table 14.2.36, p 771; Table 11-4, p 162 of the SUSTAIN 3 trial report
Abbreviation: BMI, body mass index; CI, confidence interval; SD, standard deviation; SE, standard error; sema, semaglutide
[a] Estimated using a mixed model for repeated measures (treatment and country as fixed factors and baseline value as covariate)

6.18 Treatment with semaglutide 1.0 mg was associated with a statistically significant reduction in body weight from baseline to week 56 compared with exenatide 2.0 mg. At week 56, more patients achieved a weight loss of ≥ 5% with semaglutide 1.0 mg once weekly compared with exenatide 2.0 mg once weekly. These results should also be interpreted with caution due to potential risk of bias in the trial. The ESC considered that the mean difference of 3.78 kg in weight loss may be clinically important.

6.19 The results for both HbA1c and weight loss met the nominated MCID for superiority based on statistically significant differences of > 0.3% change from baseline HbA1c, > 3.0% change from baseline body weight, > 20% more patients achieving either HbA1c < 7.0% or ≤ 6.5%; and > 20 % more patients achieving a 5% reduction in body weight. The clinical importance of the nominated MCIDs remains unclear.

6.20 The trial estimates represent a mixed dual (45%) and triple (49%) therapy population with a small proportion on other anti-diabetics (6%) that may not be generalisable to the PBS population. The submission claimed that PBS use of triple therapy is likely to be higher than for dual therapy due to stricter eligibility requirements for dual therapy use. The submission also claimed that overall population results are probably conservative in this context given numerically greater differences for both change in percentage HbA1c and body weight (kg) associated with semaglutide in triple therapy. This claim was inadequately supported as it was based on results from post-hoc subgroup analyses that may not be robust due to potential bias, no adjustment for multiplicity and potential confounding due to imbalances in baseline characteristics and use of dual and triple therapy between arms.

6.21 The submission also presented quality of life data, with results suggesting no statistically significant differences between treatment groups for domains of health status assessed by the 36-item Short Form health survey (SF-36v2). There was a

statistically significantly greater improvement in overall treatment satisfaction and self-perceived hyperglycaemia in those treated with semaglutide compared with exenatide based on results from the Diabetes Treatment Satisfaction Questionnaire (DTSQ). The results may be limited by potential bias as both patients and personnel were unblinded to treatment allocation.

SUSTAIN 7 (semaglutide 0.5 mg versus dulaglutide 0.75 mg or semaglutide 1.0 mg versus dulaglutide 1.5 mg, as dual therapy in combination with metformin only)

6.22 The SUSTAIN 7 trial was based on low and high dose semaglutide versus low and high dose dulaglutide when used as dual therapy only. The low dose formulation of dulaglutide (0.75 mg) is not available in Australia. There were no data comparing these interventions in triple therapy.

6.23 Key outcomes for change in HbA1c from the SUSTAIN 7 trial are presented in the table below. The trial was designed to compare low dose semaglutide with low dose dulaglutide; and high dose semaglutide with high dose dulaglutide. The results of the post-hoc analysis presented in PSCR comparing 0.5 mg semaglutide once weekly and 1.5 mg dulaglutide once weekly is also presented in the tables below.

Table 6: Change in HbA1c (%) and proportion of patients achieving an HbA1c target of < 7.0% from baseline to week 40 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 40, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference (95% CI)[a]
Change in HbA1c (%) from baseline to week 40 [primary outcome]					
Sema 0.5 mg	244	8.3 (0.96)	6.72 (0.06)	-1.51 (0.06)	-0.40 (-0.55, -0.25)
Dula 0.75 mg	250	8.2 (0.91)	7.12 (0.05)	-1.11 (0.05)	
Sema 1.0 mg	240	8.2 (0.92)	6.45 (0.06)	-1.78 (0.06)	-0.41 (-0.57, -0.25)
Dula 1.5 mg	251	8.3 (0.89)	6.86 (0.06)	-1.37 (0.06)	
Sema 0.5 mg	301	8.3 (1.0)	NR	-1.5 (0.1)	-0.14 (-0.30, 0.01)
Dula 1.5 mg	299	8.2 (0.9)	NR	-1.4 (0.1)	
Treatment arms	**N**	**Patients, n/N (%)**			**Odds ratio (95% CI)**
Proportion of subjects achieving an HbA1c target of < 7.0% at week 56 [exploratory outcome]					
Sema 0.5 mg	301	203/301 (68)			2.47 (1.68, 3.64)
Dula 0.75 mg	299	156/299 (52)			
Sema 1.0 mg	300	235/300 (79)			1.96 (1.28, 3.00)
Dula 1.5 mg	299	199/299 (67)			

Source: Table 2-20, p 91 of the submission; Table 14.2.50, p 766 of the SUSTAIN 7 trial report; PSCR (p6)
Abbreviation: CI, confidence interval; Dula, dulaglutide; NR, not reported; SD, standard deviation; SE, standard error; Sema, semaglutide
[a] Estimated using a mixed model for repeated measures (treatment and country as fixed factors and baseline value as covariate)

6.24 There was a statistically significant difference in HbA1c percentage reduction from baseline to week 40 with both low dose and high dose comparisons of semaglutide and dulaglutide. At week 40, more patients achieved an HbA1c of < 7.0% with semaglutide compared with dulaglutide. These results should be interpreted with caution due to the open-label trial design. The ESC considered that the treatment difference in mean change from baseline for HbA1c between semaglutide and dulaglutide was not clinically significant.

6.25 Results based on alternative datasets including a retrieved drop-out analysis (including patients who discontinued treatment) were consistent with the primary analysis in terms of statistical significance, although there was a numerical difference in point estimates of percentage HbA1c that appeared less favourable to semaglutide in both low dose (-0.28, 95% CI -0.45, -0.10) and high dose comparisons (-0.34, 95% CI -0.52, -0.15) with dulaglutide.

6.26 Both high and low dose comparisons in the primary 'on-treatment' analysis set met the glycaemic control component of the MCID nominated in the submission for superiority based on percentage HbA1c of more than 0.3% but did not consistently achieve a difference of at least 20% more patients reaching HbA1c of < 7.0%. However, results for the low dose comparison based on the retrieved drop-out analysis did not meet the nominated MCID of 0.3%; and results for the high dose comparison only marginally exceeded 0.3% and did not exceed 0.4%.

6.27 There was no direct comparison of low dose semaglutide versus high dose dulaglutide in the trial. In practice, both high and low dose semaglutide would be available as treatment alternatives to high dose dulaglutide given low dose dulaglutide is not available in Australia. The results of the post-hoc analysis comparing low dose semaglutide and high dose dulaglutide (presented in the PSCR) suggested no statistically significant difference in terms of change in percentage HbA1c. The interpretation of this analysis was difficult due to limited documentation (abstract only) and potential bias.

6.28 Results for change in body weight from the SUSTAIN 7 trial are summarised in the table below.

Table 7: Change in body weight and the proportion of subjects achieving ≥ 5% weight loss from baseline to week 40 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 40, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference (95% CI)[a]
Body weight (kg) [secondary endpoint]					
Sema 0.5 mg	244	96.4 (24.4)	90.67 (0.28)	-4.56 (0.28)	-2.26 (-3.02, -1.51)
Dula 0.75 mg	253	95.6 (23.0)	92.94 (0.27)	-2.30 (0.27)	
Sema 1.0 mg	241	95.5 (20.9)	88.70 (0.28)	-6.53 (0.28)	-3.55 (-4.32, -2.78)
Dula 1.5 mg	252	93.4 (21.8)	92.25 (0.27)	-2.98 (0.27)	
Sema 0.5 mg	301	96.4 (24.4)		-4.6 (0.3)	-1.58 (-2.35, -0.82)
Dula 1.5 mg	299	93.4 (21.8)		-3.0 (0.3)	
Body weight (%) [exploratory endpoint]					
Sema 0.5 mg	244	-	-	-4.92 (0.29)	-2.54 (-3.33, -1.75)
Dula 0.75 mg	253	-	-	-2.38 (0.28)	
Sema 1.0 mg	241	-	-	-6.92 (0.29)	-3.67 (-4.47, -2.86)
Dula 1.5 mg	252	-	-	-3.26 (0.29)	
Treatment arms	**N**	**Patients, n/N (%)**			**Odds ratio (95% CI)** or p value
Proportion of subjects achieving ≥ 5% weight loss at 40 weeks [exploratory outcome]					
Sema 0.5 mg	301	132/301 (44)			2.40 (1.65, 3.47)
Dula 0.75 mg	299	68/299 (23)			
Sema 1.0 mg	300	189/300 (63)			3.03 (2.11, 4.34)
Dula 1.5 mg	298	90/298 (30)			
Sema 0.5 mg	301	132/301 (44)			p = 0.0093
Dula 1.5 mg	299	90/298 (30)			

Source: Table 11-2, p 145; Table 11-3, p 150; Table 14.2.62, p 791; Table 14.2.103, p 884 of the SUSTAIN 7 trial report; PSCR (p6)
Abbreviation: BMI, body mass index; CI, confidence interval; Dula, dulaglutide; SE, standard error; Sema, semaglutide
[a] Estimated using a mixed model for repeated measures (treatment and country as fixed factors and baseline value as covariate)

6.29 Treatment with semaglutide was associated with a statistically significant reduction in body weight compared with dulaglutide. At week 56, more patients achieved weight loss of ≥ 5% with semaglutide compared with dulaglutide. These results should also be interpreted with caution due to potential risk of bias in the open-label trial. The ESC considered that the mean difference of 3.55 kg in weight loss between semaglutide 1.0 mg and dulaglutide 1.5 mg may be clinically important.

6.30 Results from sensitivity analyses of change in body weight (kg) using alternative datasets were consistent with the main analysis in terms of statistical significance, although there was a numerical difference with less favourable results for semaglutide for both low dose (-2.13, 95% CI -2.95, -1.30) and high dose (-3.05, 95% CI -3.85, -2.25) comparisons with dulaglutide using a retrieved drop-out dataset.

6.31 Only results for the high dose comparison met the weight loss component of the nominated MCID for superiority in the submission based on a treatment difference of > 3.0% change in body weight from baseline and at least 20% more patients achieving a 5% reduction in body weight. Results for the high dose comparison based on the retrieved drop-out dataset suggested that the difference in weight loss only marginally exceeded 3.0%.

6.32 A naïve comparison of individual arm results conducted by the evaluator suggests a small difference in body weight (%) reduction between low dose semaglutide and high

dose dulaglutide (approximately 1.7% difference) and a numerically higher proportion of patients achieving a 5% reduction in body weight (44% versus 30% respectively).

6.33 The submission also presented quality of life data, with results suggesting no statistically significant differences between treatment groups for domains of health status assessed by the 36-item Short Form health survey (SF-36v2) or treatment satisfaction based on the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Long-term benefits

6.34 The submission presented supportive data from the 2-year SUSTAIN 6 cardiovascular safety trial of semaglutide 0.5 mg or 1.0 mg versus placebo as monotherapy, in combination with 1-2 oral anti-diabetics, with or without insulin; in patients with high cardiovascular risk. The trial had limited applicability to the proposed PBS population as the majority of patients were already using insulin and were allowed to use various other treatments for glycaemic control.

6.35 Results from the primary analysis of pooled treatment arms suggest that treatment with semaglutide (0.5 mg or 1.0 mg) was not associated with an increased risk of cardiovascular events compared with placebo (HR 0.74; 95% CI 0.58, 0.95; $p < 0.001$ for non-inferiority). The results were numerically in favour of semaglutide, primarily driven by a decrease in the risk of non-fatal stroke and non-fatal myocardial infarction. There was no difference between the arms in terms of cardiovascular death. Testing for superiority for the primary outcome was conducted post-hoc and not adjusted for multiplicity.

6.36 Treatment with semaglutide was associated with an increased risk of diabetic retinopathy complications compared with placebo (HR 1.76, 95% CI 1.11, 2.78). The treatment difference between groups appeared early and continued throughout the 104 week trial duration. Treatment with semaglutide was associated with a decrease in the risk of new or worsening nephropathy compared with placebo (HR 0.64, 95% CI 0.46, 0.88). These outcomes were not included in the testing hierarchy or adjusted for multiplicity.

6.37 The submission claimed that results from the SUSTAIN 6 trial were supportive of the relationship between key surrogate outcomes of HbA1c and weight loss with cardiovascular outcomes. Key cardiovascular outcomes for other GLP-1 therapies, dulaglutide (REWIND) and exenatide once weekly (EXSCEL), were considered as supportive evidence during the evaluation. The results from these trials were generally consistent with results from the SUSTAIN 6 trial (Table 8). Superiority in terms of reduction in cardiovascular events was demonstrated for dulaglutide versus placebo, using a different trial design to SUSTAIN 6 (REWIND was designed to test superiority, larger population, longer follow-up).

Table 8: Overview of cardiovascular outcomes trials for GLP-1 therapies (semaglutide, dulaglutide, exenatide) versus placebo

Trial characteristics	SUSTAIN 6 (semaglutide)	REWIND (dulaglutide)	EXSCEL (exenatide)
Study design	Phase 3, multi-centre, double-blind, parallel-group, randomised controlled trial (event-driven trial duration, median 2.1 years)	Phase 3, multi-centre, double-blind, randomised controlled trial (event-driven trial duration, median 5.4 years)	Phase 3, multi-centre, double-blind, randomised controlled trial (event-driven trial duration, median 3.2 years)
Population	Patients with type 2 diabetes aged at least 50 years with HbA1c > 7.0% and were treatment-naïve, or had been treated with up to 2 oral anti-diabetic agents, with or without insulin; and had high cardiovascular risk (N = 3,297)	Patients with type 2 diabetes aged at least 50 years with HbA1c of 6.5 to 9.5% and were treatment-naïve or treated with up to 2 oral anti-diabetic agents, with or without basal insulin, with a BMI or ≥ 23 kg/m^2; and had high cardiovascular risk (N = 9,901)	Patients with type 2 diabetes with HbA1c of 6.5 to 10% and were treatment-naïve, or treated with up to 3 oral anti-diabetic agents or insulin either alone or in combination with up to 2 oral anti-diabetic agents, with any level of cardiovascular risk (70:30 ratio of prior CV event to no CV event) (N = 14,752)
Intervention	Fixed dose escalation over 4-8 weeks starting with 0.25 mg weekly, then: semaglutide 0.5 mg SC injection once weekly; or semaglutide 1.0 mg SC injection once weekly	Dulaglutide 1.5 mg SC injection once weekly	Exenatide 2.0 mg SC injection once weekly
Comparator	Placebo	Placebo	Placebo
Primary outcome	Time to first cardiovascular event (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) [non-inferiority]	Time to first cardiovascular event (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) [superiority]	Time to first cardiovascular event (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) [non-inferiority and superiority]
Key results (hazard ratios compared to placebo)			
Time to first cardiovascular event	Semaglutide (pooled): 108/1648 (6.6%) Placebo: 146/1649 (8.9%) HR 0.77 (0.55, 1.08)	Dulaglutide: 594/4949 (12.0%) Placebo: 663/4952 (13.4%) HR 0.88 (0.79, 0.99)	Exenatide: 839/7356 (11.4%) Placebo: 905/7396 (12.2%) HR 0.91 (0.83, 1.00)
Time to cardiovascular death	Semaglutide (pooled): 44/1648 (2.7%) Placebo: 46/1649 (2.8%) HR 1.02 (0.55, 1.86)	Dulaglutide: 317/4949 (6.4%) Placebo: 346/4952 (7.0%) HR 0.91 (0.78, 1.06)	Exenatide: 340/7356 (4.6%) Placebo: 383/7396 (5.2%) HR 0.88 (0.76, 1.02)
Time to non-fatal MI	Semaglutide (pooled): 47/1648 (2.9%) Placebo: 64/1649 (3.9%) HR 0.88 (0.52, 1.48)	Dulaglutide: 205/4949 (4.1%) Placebo: 212/4952 (4.3%) HR 0.96 (0.79, 1.16)	NR
Time to non-fatal stroke	Semaglutide (pooled): 27/1648 (1.6%) Placebo: 44/1649 (2.7%) HR 0.57 (0.31, 1.06)	Dulaglutide: 135/4949 (2.7%) Placebo: 175/4952 (3.5%) HR 0.76 (0.61, 0.95)	NR

Trial characteristics	SUSTAIN 6 (semaglutide)	REWIND (dulaglutide)	EXSCEL (exenatide)
Change in HbA1c (%)	<u>Semaglutide 0.5 mg</u> Baseline: 8.67 Endpoint: 7.61 Change: -1.09 Drift: 0.30 per year[a] <u>Placebo 0.5 mg</u> Baseline: 8.70 Endpoint: 8.26 Change: -0.44 No observable drift <u>Semaglutide 1.0 mg</u> Baseline: 8.73 Endpoint: 7.29 Change: -1.41 Drift: 0.23 per year[a] <u>Placebo 1.0 mg</u> Baseline: 8.70 Endpoint: 8.34 Change: -0.36 No observable drift Semaglutide 0.5 mg vs placebo: -0.66 Semaglutide 1.0 mg vs placebo: -1.05	<u>Dulaglutide 1.5 mg</u> Baseline: 7.3 Endpoint: NR Change: -0.46 Drift: 0.09 per year[b] <u>Placebo</u> Baseline: 7.4 Endpoint: NR Change: 0.16 Drift: 0.04 per year[b] Dulaglutide 1.5 mg vs placebo: -0.61	<u>Exenatide 2.0 mg</u> Baseline: NR Endpoint: NR Change: NR Drift: 0.10 per year[c] <u>Placebo</u> Baseline: NR Endpoint: NR Change: NR No observable drift Exenatide 2.0 mg vs placebo: -0.53
Change in body weight (kg)	<u>Semaglutide 0.5 mg</u> Baseline: 91.8 Endpoint: 88.5 Change: -3.57 <u>Semaglutide 1.0 mg</u>	<u>Dulaglutide 1.5 mg</u> Baseline: 88.7 Endpoint: NR Change: NR Dulaglutide 1.5 mg vs placebo: -1.46	<u>Exenatide 2.0 mg</u> Baseline: NR Endpoint: NR Change: NR

Trial characteristics	SUSTAIN 6 (semaglutide)	REWIND (dulaglutide)	EXSCEL (exenatide)
	Baseline: 91.8 Endpoint: 87.2 Change: -4.9 Semaglutide 0.5 mg vs placebo: -2.87 Semaglutide 1.0 mg vs placebo: -4.35		

Source: Marso 2016 publication and trial report of the SUSTAIN 6 trial; Gerstein 2018 and Gerstein 2019 publications (plus supplementary appendix) of the REWIND trial, Holman 2017 publication of the EXSCEL trial

Abbreviations: BMI, body mass index; MI, myocardial infarction; NR, not reported

[a] Semaglutide estimates based on the nadir of HbA1c (%) at 4 months and endpoint; Figure 12-1 of the SUSTAIN 6 trial report

[b] Dulaglutide estimate based on the nadir of HbA1c (%) at 3 months and endpoint; Placebo estimate based on HbA1c (%) from baseline to endpoint; Figure 4, Gerstein 2019 publication

[c] Exenatide estimate based on the nadir of HbA1c (%) at 6 months and endpoint; Figure 1, Holman 2017 publication

6.38 Longer-term data from the SUSTAIN 6 trial indicate the differences in HbA1c between low and high dose semaglutide versus placebo remained statistically significant over 2 years, but the difference attenuated over time. The data suggest a drift in HbA1c from a nadir of 4 months to the 2-year endpoint in both low (from 7.1% to 7.6%) and high dose semaglutide (from 6.9% to 7.3%) arms. There was no observable drift in the placebo arm. It was unclear whether the observed drift was due to loss of efficacy, issues with compliance or disease progression. Data from the REWIND and EXSCEL trials suggest smaller drifts in HbA1c for both dulaglutide (nadir of 6.6% at 5 months to 7.0% at 5 years) and exenatide once weekly (nadir of 7.3% at 6 months to 7.7% at 5 years). There was a relatively small drift in the placebo arm of the REWIND trial and no observable drift in the placebo arm of the EXSCEL trial.

6.39 Weight loss results from the SUSTAIN 6 trial indicate that treatment effects with both low and high dose semaglutide were sustained over 2 years. These results were consistent with results for dulaglutide from the REWIND trial showing sustained weight loss over 5 years. Although weight loss associated with exenatide in the EXSCEL trial remained statistically significant compared with placebo, there was a small drift in weight for both arms over 5 years (median follow-up of 3.2 years). The ESC considered that the long term impact of weight loss achieved is unknown, particularly when treatment was stopped/switched. The Pre-PBAC Response acknowledged that it remains unclear whether these outcomes would be maintained over time horizons greater than 1-2 years and/or in the event of treatment switching or intensification, given currently available clinical data.

<u>Assessment of differences between the trial settings and the Australian setting</u>

6.40 The submission claimed that patient characteristics in all included trials were broadly similar to the Australian PBS population with type 2 diabetes in relation to key baseline demographic and disease characteristics. The submission did not adequately address the applicability of these trials to the PBS population. In particular, it was unclear whether baseline HbA1c levels and BMI from the SUSTAIN trials are representative of the requested PBS population.

6.41 Baseline HbA1c levels in the key trials were relatively high (ranging from 8.2% to 8.36%) compared with published treatment targets for glycaemic control (6.5% or 7.0%) and were higher than those in the Australian community setting who would become suitable for GLP-1 therapies. Post-hoc subgroup analyses by baseline HbA1c levels using data from the SUSTAIN 3 (Petri et al 2018) and SUSTAIN 7 trials (abstract only, Pratley 2018) indicated that the relative change in HbA1c with semaglutide remained statistically significantly greater than the comparator arms, however, the absolute changes were smaller in patients with lower baseline HbA1c, and thus likely to be smaller in Australian clinical practice.

6.42 The trial populations included a relatively high proportion of obese patients (60-70%) which may not be representative of clinical practice. Australian studies suggest that the majority of patients are overweight rather than obese (Shamshirgaran 2018 and Fremantle Diabetes studies), therefore, trial-based BMI may overestimate the baseline BMI in the PBS population. A post-hoc subgroup analysis of weight loss by baseline BMI suggests numerically lower changes in body weight with semaglutide in categories of normal or overweight compared with those who are obese or morbidly obese (Ahren et al 2018). The ESC considered that the proportion of obese patients in the studies was greater than the Australian setting and that this may impact on the extent of weight loss that could be achieved.

6.43 The submission noted that the SUSTAIN trials used fixed dose treatment regimens while the draft product information recommends flexible dose titration to achieve glycaemic control. The submission claimed that the majority of patients in clinical practice will titrate to the highest dose (1.0 mg) although it was acknowledged that long term treatment with lower dose semaglutide (0.5 mg) was also plausible. The ESC considered this claim was not reasonable, as the dose of semaglutide in practice will likely vary based on glycaemic targets and the tolerability of treatments in individual patients (e.g. the fixed dose 1.0 mg may overestimate both the mean reduction in HbA1c and the incidence of adverse events as not all patients would require up-titration).

6.44 The submission noted that while both low dose and high dose semaglutide achieve statistically significant results in terms of HbA1c and weight loss, high dose semaglutide is associated with numerically greater changes in these measures. There was no formal comparison of efficacy and safety between the two doses. Although the magnitude of difference between the doses remains unclear, the absolute change in HbA1c and weight loss is likely to be lower with low dose semaglutide than with high dose semaglutide.

6.45 There were sparse data for both low and high dose semaglutide when used as dual therapy with sulfonylurea due to limited numbers of patients on sulfonylurea monotherapy at baseline in the trials. There were no data for semaglutide treatment as add-on therapy to patients using either metformin or sulfonylurea monotherapy at baseline due to a contraindication or intolerance to either treatment, which is part of the eligibility criteria for semaglutide use as dual therapy under the proposed restriction. The ESC agreed with the assertion of the sponsor in the PSCR that is was unreasonable to demonstrate all comparisons due to the large number of possible combinations.

Comparative harms

6.46 Safety data from the short-term key trials (SUSTAIN 3 and 7) are presented below based on the 'on-treatment without rescue medication' observation periods. The in-trial observation period including all trial-related events and assessments were used

for supportive analyses only. The trial reports noted no clinically relevant differences in safety observations between the two observation periods.

6.47 The table below summarises the overall safety data from the SUSTAIN 3 trial of high dose semaglutide versus exenatide once weekly (56 weeks).

Table 9: Summary of key adverse events in the SUSTAIN 3 trial (on-treatment without rescue medication analysis)

Adverse event	Semaglutide 1.0 mg N=404		Exenatide 2.0 mg N=405	
	Incidence, n (%)	Event rate per 100 patient-years	Incidence, n (%)	Event rate per 100 patient-years
Any adverse event	303 (75.0)	374.7	309 (76.3)	370.4
Serious adverse event	38 (9.4)	12.6	24 (5.9)	6.6
Discontinuation due to adverse event	38 (9.4)	11.6	29 (7.2)	11.5
Deaths	2 (0.5)	0.5	0 (0)	0
Adverse events of special interest				
Gastrointestinal adverse event	169 (41.8)	133.1	135 (33.3)	83.6
Injection-site nodules	0 (0)	0	49 (12.1)	13.5
Hepatobiliary disorders	8 (2.0)	1.9	3 (0.7)	0.7
Severe hypoglycaemia or blood glucose-confirmed symptomatic	29 (7.2)	9.9	28 (6.9)	11.3

Source: Table 14.3.1.1, p 1060; Table 14.3.1.51, p 1249; Table 12-13, p 223; Table 12-9, p 216 of the SUSTAIN 3 trial report
Note: Diabetic retinopathy was not reported as an adverse event of special interest in the trial

6.48 The overall incidence of any adverse event was similar between treatment arms. There was a higher rate of serious adverse events with semaglutide arm compared with exenatide primarily due to differences in gastrointestinal disorders and neoplasms. More patients treated with semaglutide discontinued treatment prematurely compared to exenatide, primarily due to gastrointestinal disorders. Two deaths occurred in the semaglutide arm that were unrelated to treatment.

6.49 The most frequently reported class of adverse events was gastrointestinal disorders (nausea, diarrhoea, vomiting) followed by nasopharyngitis and headache. Semaglutide was associated with a higher rate of gastrointestinal adverse events (majority were of mild to moderate severity) whereas exenatide was more commonly associated with injection-site nodules. The rate of severe hypoglycaemia events with exenatide was higher than with semaglutide, however, this may be an effect of the imbalance in dual/triple therapy use between arms (more patients on triple therapy in the exenatide arm).

6.50 Overall safety data from the low and high dose arms for semaglutide and dulaglutide from the SUSTAIN 7 trial (40 weeks) are summarised in the table below.

Table 10: Summary of key adverse events in the SUSTAIN 7 trial (on-treatment without rescue medication analysis)

Adverse event	Semaglutide 0.5 mg N=301		Dulaglutide 0.75 mg N=299		Semaglutide 1.0 mg N=300		Dulaglutide 1.5 mg N=299	
	n (%)	Rate / 100 patient-years	n (%)	Rate / 100 patient-years	n (%)	Rate / 100 patient-years	n (%)	Rate / 100 patient-years
Any adverse event	204 (68)	412.7	186 (62)	326.2	207 (69)	439.7	221 (74)	402.6
Serious adverse event	17 (6)	9.8	24 (8)	13.8	23 (8)	11.7	22 (7)	13.9
Discontinuation due to adverse event	24 (8)	19.7	14 (5)	9.4	29 (10)	28.6	20 (7)	21.5
Deaths	1 (<1)	0.4	2 (1)	0.8	1 (<1)	0.4	2 (1)	2.0
Adverse events of special interest								
GI adverse event	129 (43)	168.3	100 (33)	104.5	133 (44)	215.7	143 (48)	165.4
Injection-site reactions	4 (1)	2.1	4 (1)	3.7	6 (2)	2.6	8 (3)	7.2
Gallbladder disorders	2 (1)	0.9	4 (1)	1.6	4 (1)	2.2	8 (3)	3.8
Severe hypoglycaemia or blood glucose-confirmed symptomatic	2 (1)	1.3	3 (1)	1.2	5 (2)	3.0	5 (2)	2.1
Diabetic retinopathy	2 (1)	0.8	2 (1)	0.8	2 (1)	0.8	3 (1)	1.2

Source: Table 4, Pratley 2019 publication for the SUSTAIN 7 trial; Table 12-12, p 213 of the SUSTAIN 7 trial report
Abbreviation: GI, gastrointestinal

6.51 The overall incidence of any adverse event was similar between treatment arms, however, the rate of adverse events was lower with the dulaglutide 0.75 mg dose. The incidence of serious adverse events was similar between arms. There were six deaths reported in the trial, all of which were assessed as unlikely to be related to treatments.

6.52 The most frequently reported class of adverse events was gastrointestinal disorders (nausea, diarrhoea, vomiting) followed by nasopharyngitis and headache. The rate of gastrointestinal adverse events was highest in the semaglutide 1.0 mg arm, similar between the semaglutide 0.5 mg and dulaglutide 1.5 mg arms and lowest in the dulaglutide 0.75 mg arm. The rates of other most commonly reported adverse events were similar between treatment arms. There were no observable differences in events of diabetic retinopathy between arms. However, the total number of events was small as patients with known proliferative retinopathy or maculopathy requiring acute treatment were excluded from the trial.

6.53 An expanded assessment of harms identified important risks including gastrointestinal adverse events (nausea, vomiting, diarrhoea), acute gallstone disease (cholelithiasis), and severe hypoglycaemia in combination with sulfonylurea and/or insulin and diabetic retinopathy complications. Important potential risks include acute pancreatitis, serious allergic reactions, medullary thyroid cancer and pancreatic cancer. Missing information included use in pregnancy and lactation as well as patients with severe hepatic impairment.

6.54 Treatment with semaglutide is associated with a rapid initial decline in blood glucose, and analyses from the SUSTAIN 6 trial indicate that this is the most likely mechanism underlying the increased risk of diabetic retinopathy complications with semaglutide

treatment. This effect was primarily seen in the subset of patients with longer duration of diabetes, history of diabetic retinopathy at baseline, a high baseline HbA1c and insulin use. A Phase 3 trial is currently ongoing to evaluate the long term effects of semaglutide on diabetic retinopathy (FOCUS, NCT03811561; expected completion in 2025).

6.55 Gastrointestinal adverse events are a known GLP-1 receptor-mediated action and a known class effect of other GLP-1 analogues. However, the rate of gastrointestinal adverse events was higher with semaglutide compared to other GLP-1 comparators as well as all comparators based on a pooled analysis from the broader SUSTAIN trial program provided in the Periodic Safety Update Report (1 December 2018 to 31 May 2019). The ESC considered that the high rates of gastrointestinal adverse events for semaglutide may affect titration to 1.0 mg. The difference in HbA1c and weight loss is attenuated at the lower semaglutide dose.

6.56 The submission presented selected safety data for hypoglycaemia adverse events from the SUSTAIN 4 trial (open-label trial of semaglutide 0.5 mg or 1.0 mg versus insulin glargine). The data suggested that the rate of hypoglycaemic events were higher in the insulin glargine arm compared with both strengths of semaglutide. The data were only used to inform hypoglycaemia event rates for the insulin glargine arm in the economic model. Data comparing the full safety profiles of semaglutide versus insulin glargine were not presented in the submission.

6.57 The submission presented a post-hoc, chi-squared analysis of gastrointestinal adverse events and weight loss targets for treatment arms of semaglutide, exenatide and dulaglutide from the SUSTAIN 3 and 7 trials. The submission claimed the results suggested no correlation between the greater weight loss achieved with semaglutide and the increased gastrointestinal adverse events. This claim was inadequately supported as the analysis did not appear to be robust. This was a simple analysis that did not control for other factors associated with weight loss (e.g. age, sex, baseline weight). The semaglutide group in the analysis was also based on inappropriately combined, unadjusted data from trials with different populations.

6.58 Other studies using pooled data from the broader SUSTAIN trial program and another based on other GLP-1 studies (DURATION trial program for exenatide once weekly) suggest that gastrointestinal adverse events are a likely contributor to the weight loss effect associated with GLP-1 analogues (Ahren et al 2018 and Horowitz et al 2016). However, the magnitude of weight loss that can be attributed to the occurrence of gastrointestinal events remains unclear.

Benefits/harms

6.59 On the basis of direct evidence presented in the submission, for every 100 patients with type 2 diabetes treated with semaglutide 1.0 mg once weekly in comparison to exenatide once weekly, as dual or triple therapy with metformin and/or sulfonylurea:

- Approximately 27 more patients would achieve an HbA1c target of less than 7% over 56 weeks
- Approximately 35 more patients would achieve at least 5% weight loss over 56 weeks
- Approximately 50 more gastrointestinal adverse events would occur over 12 months
- No patients would experience an injection-site nodule over 12 months

6.60 On the basis of direct evidence presented in the submission, for every 100 patients with type 2 diabetes treated with semaglutide 1.0 mg once weekly in comparison to dulaglutide 1.5 mg once weekly as dual therapy with metformin:

- Approximately 12 more patients would achieve an HbA1c target of less than 7% over 40 weeks
- Approximately 33 more patients would achieve at least 5% weight loss over 40 weeks
- Approximately 50 more gastrointestinal adverse events would occur over 12 months

Clinical claim

6.61 The submission described semaglutide 1.0 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared with exenatide 2.0 mg once weekly when used as dual or triple therapy with metformin and/or sulfonylurea. The ESC considered the efficacy claim was reasonable in terms of statistically significant change in HbA1c and weight loss. However, the clinical importance of these differences remains unclear. In terms of safety, high dose semaglutide was potentially inferior compared to exenatide once weekly due to the increased risk of gastrointestinal adverse events.

6.62 The submission did not make a clinical claim for semaglutide 0.5 mg versus exenatide 2.0 mg once weekly in dual or triple therapy with metformin and/or sulfonylurea.

6.63 The submission described semaglutide 0.5 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared with dulaglutide 1.5 mg once weekly in dual therapy with metformin or sulfonylurea. The efficacy claim was inadequately supported by the data. Low dose semaglutide was potentially non-inferior in terms of change in HbA1c and weight loss and safety compared with dulaglutide 1.5 mg once weekly.

6.64 The submission described semaglutide 1.0 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared with dulaglutide 1.5 mg once weekly in dual therapy with metformin or sulfonylurea. The efficacy claim may be reasonable in terms of statistically significant change in HbA1c and weight loss. However, it was unclear whether the incremental gain in reduction in HbA1c and body weight was clinically important. In terms of safety, high dose semaglutide was non-inferior to dulaglutide 1.5 mg.

6.65 The submission did not make a clinical claim for semaglutide 0.5 mg or 1.0 mg once weekly versus dulaglutide 1.5 mg once weekly in triple therapy with metformin and sulfonylurea.

6.66 The ESC considered there was insufficient evidence of superiority of semaglutide over both comparators, but particularly dulaglutide, given the gaps in the clinical data presented. This is a particular issue if there is higher use of 0.5 mg semaglutide as a result of the gastrointestinal side effects associated with 1.0 mg semaglutide. It was unclear (in the context of previous PBAC considerations) that the comparative HbA1c and weight outcomes demonstrated in the SUSTAIN trials demonstrated superior and clinically important outcomes in the longer term for semaglutide over the comparators. An increased focus on CVD outcomes is warranted but no comparative data between semaglutide and dulaglutide was provided.

6.67 As there is no acceptable basis for the superiority claim over dulaglutide, the ESC concluded that semaglutide was likely non-inferior in terms of efficacy to dulaglutide.

6.68 The PBAC considered that the claim of superior comparative effectiveness was reasonable in relation to exenatide, although the sustainability and clinical importance of these benefits long-term remained unclear.

6.69 The PBAC considered the claim of superior comparative effectiveness was not adequately supported by the data in relation to dulaglutide.

6.70 The PBAC considered that the claim of non-inferior comparative safety was reasonable in relation to exenatide or dulaglutide, but may be inferior to exenatide based on gastrointestinal events.

Economic analysis

6.71 The submission presented a modelled economic evaluation of semaglutide 1.0 mg versus exenatide once weekly (based on the SUSTAIN-3 trial) as dual/triple therapy for type 2 diabetes. The submission also presented a supportive modelled economic evaluation of semaglutide 0.5 mg or 1.0 mg versus dulaglutide once weekly (based on the SUSTAIN-7 trial) as dual therapy for type 2 diabetes. The economic evaluations were based on changes in HbA1c, BMI and other biomarkers reported in the clinical trials as well as other modelled variables. The economic evaluations were presented as cost-utility analyses.

6.72 The cost effectiveness of semaglutide 0.5 mg compared to exenatide once weekly was unknown as no economic analysis was presented in the submission. Additionally, the cost effectiveness of semaglutide versus dulaglutide as triple therapy was also unknown as no analysis was presented in the submission.

6.73 The clinical data presented in the submission did not adequately support a superiority claim for semaglutide 0.5 mg compared with dulaglutide 1.5 mg once weekly and therefore a cost-utility analysis may not be appropriate for this comparison. The ESC considered that a cost-minimisation to dulaglutide was more appropriate.

Table 11: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	10 years
Methods used to generate results	IHE DCM model; Markov cohort analysis
Treatments	Sequential treatment with semaglutide 0.5 mg, semaglutide 1.0 mg, exenatide once weekly or dulaglutide once weekly followed by insulin
Health states	Seven independent diabetes complication modules (eye disease, lower extremity disease, kidney disease, ischaemic heart disease, myocardial infarction, stroke, heart failure), one adverse event module (hypoglycaemia) and death. Overall, there were approximately 12,000 health state combinations
Cycle length	1 year (with half-cycle correction)
Transition probability	Progression of biomarkers (HbA1c, BMI, blood pressure, heart rate, lipid profile and renal function) based on key clinical trial and supporting data Treatment decisions and pathways based on local guidelines and clinical practice Complication and mortality rates based on type 2 diabetes risk equations
Discount rate	5% for costs and outcomes
Software package	Excel 2016 with Visual Basic plugins

Source: Table 3-1 (p 161) of the submission
Abbreviations: IHE DCM, Institute of Health Economics Diabetes Cohort Model

6.74 Patients start the model with a variety of different diabetes complications, dependent on the baseline patient characteristics. During each cycle, a patient simultaneously goes through each of the modules and can experience up to one event from each of the diabetes complication modules and multiple events from the adverse event module. Patients may also die from diabetes complications or other causes.

6.75 A brief summary of the states included in each of the modules is presented below:

- Eye diseases: None, background retinopathy, proliferative retinopathy, macular oedema, macular oedema and proliferative retinopathy, severe visual loss
- Lower extremity disease: None, symptomatic neuropathy, peripheral vascular disease, lower extremity amputation, history of lower extremity amputation
- Kidney disease: None, microalbuminuria, macroalbuminuria, end stage renal disease
- Ischaemic heart disease: None, ischaemic heart disease

- Myocardial infarction: None, first myocardial infarction, history of single myocardial infarction, subsequent myocardial infarction, history of multiple myocardial infarction
- Stroke: None, first stroke, history of single stroke, subsequent stroke, history of multiple stroke
- Heart failure: None, heart failure

6.76 All patients begin the model with uncontrolled diabetes. Patients are initially treated with GLP-1 therapies until their HbA1c levels increase to 8% after which they switch to insulin glargine. Patients are then assumed to remain on fixed dose insulin glargine until their HbA1c levels again increase to 8% after which they switch to an insulin intensification regimen (insulin glargine with insulin aspart). The ESC considered that in practice HbA1c levels are often greater than 8% before switching to insulin.

6.77 The use of a sequential treatment approach has major consequences for the interpretation of the economic model. The economic model appropriately assumes that patients who are uncontrolled (based on HbA1c levels) on one treatment regimen would simply be switched to another effective treatment regimen. This approach minimises the impact of any specific therapy on the incidence of microvascular and macrovascular complications. As a consequence, the incremental differences that drive the model are based on benefits other than diabetes complications such as weight loss, delay in insulin use and reduced hypoglycaemia events. The ESC considered that a sequential treatment approach was reasonable, although the sustained incremental benefit and long-term plateau in BMI after switching to insulin was not plausible or supported by clinical evidence.

6.78 Due to the sequential structure of the model, the evaluation focused on the key drivers of the modelled benefit rather than the more traditional focus on diabetes complications. The table below summarises the key drivers of the modelled benefits included in the economic analyses. The ESC noted the relative incremental QALYs from micro- and macrovascular complications was considerably smaller than was estimated for insulin use, weight change and hypoglycaemia.

Table 12: Key drivers of the modelled benefits included in the economic analyses

Analyses	Incremental differences in QALYs		
	SEMA 1.0 mg vs EXE	SEMA 0.5 mg vs DULA	SEMA 1.0 mg vs DULA
Insulin use	0.079	0.036	0.069
Weight change	0.074	0.031	0.068
Hypoglycaemia	0.053	0.023	0.052
Micro- and macrovascular complications	0.006	-0.001	0.004

Source: IHE DCM 4.3 Australia Excel model with corrections for errors in BMI change with insulin, hypoglycaemia event rates and sulfonylurea drug costs with insulin; and removing BMI rounding in calculation of overweight disutility
Abbreviations: QALY, quality-adjusted life year

6.79 During the evaluation, a number of errors were identified and corrected in the economic analyses. However, due to the inherent complexity of the model (approximately 12,000 combinations of health states, constructed from a large

number of inputs with 17,000 lines of Visual Basic code) it was not possible during the evaluation period to check and validate all the modelled estimates. The evaluation focused instead on checking the key model inputs.

6.80 Key drivers of the economic model are summarised in the table below.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Delay in insulin use	The delay in insulin use was dependent on modelled baseline HbA1c, treatment effects, biomarker drift and treatment thresholds. Modelled baseline HbA1c was based on the SUSTAIN 3, 7 trials. Baseline HbA1c levels in the key trials were relatively high compared with published treatment targets for glycaemic control and may not be representative of the target PBS population. The treatment effects of GLP-1 therapies on biomarkers were estimated based on the SUSTAIN 3, 7 trials. The absolute changes reported in the SUSTAIN trials are dependent on baseline values that may be higher than the target PBS population. The economic model incorporated an upward drift in HbA1c over time with GLP-1 therapies based on the longer-term SUSTAIN 6 trial. The SUSTAIN 6 trial had limited applicability to the target PBS population as the majority of patients were already using insulin and were allowed to use various other treatments for glycaemic control. Longer-term trials for other GLP-1 therapies have reported substantially lower HbA1c drift estimates compared to the SUSTAIN 6 trial. The ESC considered that the HbA1c drift was higher than other estimates and that the ICER was sensitive to this assumption. The submission assumed patients would switch to insulin therapy after their HbA1c levels reach a specific threshold based on local expert advice and previous published economic models. The submission assumed that insulin therapy would be intensified if patients reached the same threshold again. It was unclear whether the nominated thresholds were reasonable as they were substantially higher than the treatment targets for glycaemic control in published treatment guidelines and it was unclear whether physicians would wait until a patient's HbA1c reached these thresholds before initiating insulin therapy.	High, direction unclear
Change in BMI over time	The change in BMI over time was dependent on modelled baseline BMI, treatment effects, delay in insulin use and residual treatment effects. Modelled baseline BMI and treatment effects of GLP-1 therapies were based on the SUSTAIN 3, 7 trials. The trial populations included a relatively high proportion of obese patients which may not be representative of clinical practice (Australian studies suggest that the majority of patients are overweight rather than obese). The SUSTAIN clinical trials generally showed that patients with higher baseline BMI values had larger absolute reductions in BMI with treatment (Ahren et al 2018). The delay in insulin was modelled based on other variables and was highly uncertain (see above). The submission assumed that incremental differences in BMI between GLP-1 therapies would be maintained after patients switch to insulin therapy. This assumption was not justified in the submission. The ESC noted that the PBAC has previously considered that the assumption of ongoing benefits after switching to insulin is inappropriate (exenatide once weekly, July 2011 PSD).	High, favours semaglutide
Hypoglycaemia events	Hypoglycaemia event rates with GLP-1 therapies were estimated based on the SUSTAIN 3 and SUSTAIN 7 trials.	High, favours semaglutide

Description	Method/Value	Impact
	Hypoglycaemia event rates with insulin were estimated based on the SUSTAIN-4 trial (open-label RCT comparing semaglutide with insulin glargine). The estimated hypoglycaemia event rates used in the model appear to be highly uncertain with major differences between trial populations and inconsistent patterns between semaglutide dose strengths. In particular, hypoglycaemia rates observed with semaglutide treatment in the SUSTAIN 4 trial were substantially higher than the SUSTAIN 3 and 7 trials. This suggests that the study population in the SUSTAIN 4 trial was at higher risk of hypoglycaemia compared to the other trials. Therefore, comparing hypoglycaemia rates between trials (rather than within trials) is likely to overestimate the incremental difference between semaglutide and insulin therapy. Hypoglycaemia disutility values were based on a published systematic review (Beaudet et al 2014). Estimates were based on fear of hypoglycaemia in patients with a symptomatic episode requiring or not requiring external intervention in past 3 months. There were important differences in hypoglycaemia severity definitions between the trial data and the utility data (mild events: asymptomatic vs. symptomatic episodes without external intervention; moderate event: symptomatic episodes without external intervention vs. symptomatic episodes with/without external intervention). Severe events appeared to be consistent between data sources. The submission assumed that these disutility values could be applied to patients who experienced one or more hypoglycaemia event in a 12 month period. This assumption may not be reasonable as the impact of each hypoglycaemia episode is likely to diminish over time. The ESC noted that PBAC had not previously accepted arguments for disutilities due to fear of hypoglycaemic events as these may only apply to a small sub-set of hypoglycaemic events (see insulin detemir and insulin glargine PSDs, March 2006). The submission estimated hypoglycaemia event costs based on the assumption that mild episodes would be managed by GPs, moderate episodes would require an emergency room visit and severe episodes would require hospitalisation. These assumptions were not adequately justified and were not consistent with the trial data used to inform hypoglycaemia rates. In the trial data, only severe episodes required external intervention which could include the administration of carbohydrate, glucagon or other corrective action (and therefore may not require hospitalisation).	
Insulin disutility	Insulin disutility was estimated based on the CODE-2 study (large cross-sectional survey of Type 2 diabetes patients in Europe). Typically, the disutility associated with insulin treatment is associated with fear of hypoglycaemia, weight gain, injection burden and more advanced disease. However, as the model already incorporates utility impacts for hypoglycaemia, weight gain and advanced disease there is the potential for substantial double counting between utility estimates. Additionally, the CODE-2 study did not capture data on patients using injectables other than insulin (e.g. GLP-1 therapies) and therefore may overestimate the impact of injection burden. A direct comparison of semaglutide and insulin glargine in the open-label SUSTAIN-4 trial indicated that treatment with semaglutide was associated with improvements in treatment satisfaction and some small improvements in quality of life measures (role	High, favours semaglutide

Description	Method/Value	Impact
	emotional and general health using the SF-36 measure for semaglutide 1.0 mg only). However, the results of the SUSTAIN-4 trial also indicated that semaglutide was associated with a higher incidence of adverse events compared to insulin glargine (primarily due to nausea, vomiting and diarrhoea). Overall, the results of the SUSTAIN-4 trial do not support a large utility difference between semaglutide treatment and insulin therapy.	
Time horizon	The submission nominated a 10 year time horizon for the economic analysis on the basis that this represented a reasonable compromise between the lifelong duration of the disease, the potential duration of GLP-1 therapy (3-7 years), the potential longer term benefits arising from delayed insulin use, the limited extent of follow up in the relevant randomised trials and likely future evolutions in the management of type 2 diabetes. The appropriateness of the time horizon is highly dependent on the potential duration of GLP-1 therapy which in turn is dependent on baseline HbA1c, treatment effects, biomarker drift and treatment thresholds. A number of plausible variations in these characteristics can lead to substantially longer or shorter GLP-1 treatment durations. The ESC considered that the 10 year time horizon was appropriate based on the submission's justification.	High, direction unclear

6.81 The model included additional differences in blood pressure, heart rate, lipid profile and renal function between GLP-1 therapies (semaglutide, exenatide, dulaglutide). The inclusion of these treatment effects was not adequately justified as there was no statistically significant difference between treatment arms for most of these variables in the SUSTAIN clinical trials. The ESC considered that the assumption that these biomarkers revert back to baseline when patients switch from GLP-1 to insulin was inappropriate, however their inclusion in the economic model did not significantly impact the ICER.

6.82 The model assumed that there would be no other differences in adverse events between GLP-1 therapies. This assumption may not be reasonable as semaglutide appears to have a higher incidence of gastrointestinal events compared to other GLP-1 therapies.

6.83 The submission also assumed there would be no other differences in adverse events between semaglutide and insulin glargine. This assumption was not reasonable. In the SUSTAIN 4 trial, semaglutide was associated with both a higher incidence and rate of adverse events compared to insulin glargine. These differences were mainly driven by the occurrence of gastrointestinal events (i.e. nausea, diarrhoea and vomiting).

6.84 The results of the modelled economic evaluation based on published prices are summarised below.

6.85 During the evaluation, the base case economic analysis was respecified to include a correction in BMI change with insulin, a correction in sulfonylurea drug costs with insulin, a correction in hypoglycaemia event rates, and removal of BMI rounding for the purpose of calculating the overweight disutility.

Table 14: Results of the economic evaluation (semaglutide vs exenatide once weekly)

Component	Semaglutide 1.0 mg	Exenatide once weekly	Increment
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	5.661	5.446	0.215
		Incremental cost per QALY gained	$ [redacted]

Source: IHE DCM 4.3 Australia Excel model with corrections for errors in BMI change with insulin, hypoglycaemic event rates and sulfonylurea drug costs with insulin; and removing BMI rounding in calculation of overweight disutility

6.86 Based on the economic model, treatment with semaglutide was associated with a cost per QALY gained of less than $15,000 compared to exenatide once weekly when used as part of dual/triple therapy for type 2 diabetes. Over the 10-year time horizon of the economic model, treatment with semaglutide was associated with a 2 year delay in the time to insulin, an average 1.41 kg/m^2 reduction in BMI and 3 fewer hypoglycaemia events per patient compared to exenatide once weekly. There were minimal differences in microvascular and macrovascular complications between treatment arms. The ESC noted that key drivers of QALY gain were insulin therapy, weight and hypoglycaemia. The ESC noted that the insulin therapy utility decrement was derived through a cross sectional analysis of UK data, valued using the UK algorithm. The ESC noted that the QALY gains from weight change were affected by the assumption of long-term difference and considered that this was not justified. The ESC noted that the definition of hypoglycaemia in the trials differed from the valuation study and considered that this probably biased in favour of semaglutide.

Table 15: Results of the economic evaluation (semaglutide vs dulaglutide once weekly)

Component	Semaglutide 0.5 mg	Dulaglutide once weekly	Increment
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	5.796	5.706	0.090
		Incremental cost per QALY gained	$ [redacted]
Component	**Semaglutide 1.0 mg**	**Dulaglutide once weekly**	**Increment**
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALYs	5.900	5.706	0.194
		Incremental cost per QALY gained	$ [redacted]

Source: IHE DCM 4.3 Australia Excel model with corrections for errors in BMI change with insulin, hypoglycaemia event rates and sulfonylurea drug costs with insulin; and removing BMI rounding in calculation of overweight disutility

6.87 Based on the economic model, treatment with semaglutide 0.5 mg was associated with a cost per QALY gained of less than $15,000 compared to dulaglutide once weekly when used as part of dual therapy for type 2 diabetes. Over the 10-year time horizon of the economic model, treatment with semaglutide 0.5 mg was associated with a 1 year delay in the time to insulin, an average 0.59 kg/m^2 reduction in BMI and 1 fewer hypoglycaemia events per patient compared to dulaglutide once weekly. There were minimal differences in microvascular and macrovascular complications between treatment arms.

6.88 Treatment with semaglutide 1.0 mg was associated with a cost per QALY gained of less than $15,000 compared to dulaglutide once weekly when used as part of dual therapy for type 2 diabetes. Over the 10-year time horizon of the economic model, treatment with semaglutide 1.0 mg was associated with a 2 year delay in the time to insulin, an

average 1.31 kg/m^2 reduction in BMI and 3 fewer hypoglycaemia events per patient compared to dulaglutide once weekly. There were minimal differences in microvascular and macrovascular complications between treatment arms.

6.89 The results of key sensitivity analyses are summarised below.

Table 16: Results of sensitivity analyses

Analyses	ICER per QALY		
	SEMA 1.0 mg vs EXE	SEMA 0.5 mg vs DULA	SEMA 1.0 mg vs DULA
Base case	$ [redacted]	$ [redacted]	$ [redacted]
Time horizon (base case 10 years)			
5 years	$ [redacted]	$ [redacted]	$ [redacted]
20 years	$ [redacted]	$ [redacted]	$ [redacted]
Baseline HbA1c			
8.0%	$ [redacted]	$ [redacted]	$ [redacted]
7.5%	$ [redacted]	$ [redacted]	$ [redacted]
HbA1c drift			
+0.15 on GLP-1 therapies	$ [redacted]	$ [redacted]	$ [redacted]
+0.10 on GLP-1 therapies	$ [redacted]	$ [redacted]	$ [redacted]
+0.10 on insulin	$ [redacted]	$ [redacted]	$ [redacted]
Semaglutide treatment effects			
HbA1c reduction Upper CI	$ [redacted]	$ [redacted]	$ [redacted]
HbA1c reduction Lower CI	$ [redacted]	$ [redacted]	$ [redacted]
BMI reduction Upper CI	$ [redacted]	$ [redacted]	$ [redacted]
BMI reduction Lower CI	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia event rates increased by 20%	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia event rates decreased by 20%	$ [redacted]	$ [redacted]	$ [redacted]
Insulin treatment effects			
HbA1c reduction Upper CI	$ [redacted]	$ [redacted]	$ [redacted]
HbA1c reduction Lower CI	$ [redacted]	$ [redacted]	$ [redacted]
BMI increase Lower CI	$ [redacted]	$ [redacted]	$ [redacted]
BMI increase Upper CI	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia event rates doubled	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia event rates halved	$ [redacted]	$ [redacted]	$ [redacted]
Other treatment effects			
Remove other biomarker treatment effects[a]	$ [redacted]	$ [redacted]	$ [redacted]
No residual treatment effects after both arms switched to insulin (set same as comparator)	$ [redacted]	$ [redacted]	$ [redacted]
Diabetes complications			
Remove event costs, states costs and disutility loss	$ [redacted]	$ [redacted]	$ [redacted]
Treatment-related disutility values			
Decrease insulin disutility to 0.000	$ [redacted]	$ [redacted]	$ [redacted]
Increase insulin disutility to -0.100	$ [redacted]	$ [redacted]	$ [redacted]
Decrease BMI disutility to 0.000 per 1 BMI increase	$ [redacted]	$ [redacted]	$ [redacted]
Increase BMI disutility to -0.010 per 1 BMI increase	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia disutility values doubled	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia disutility values halved	$ [redacted]	$ [redacted]	$ [redacted]
Treatment-related costs			
Hypoglycaemia costs doubled	$ [redacted]	$ [redacted]	$ [redacted]
Hypoglycaemia costs removed	$ [redacted]	$ [redacted]	$ [redacted]

Source: IHE DCM 4.3 Australia Excel model with corrections for errors in BMI change with insulin, hypoglycaemia event rates and sulfonylurea drug costs with insulin; and removing BMI rounding in calculation of overweight disutility

Abbreviations: CI, confidence interval; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

[a] Differences in blood pressure, heart rate, lipid profile and renal function between GLP-1 therapies

The redacted table shows ICERs in the range of less than $15,000/QALY - $45,000/QALY.

6.90 The results of the sensitivity analyses indicated that the comparison of semaglutide versus exenatide once weekly was most sensitive to hypoglycaemia event rates, insulin disutility and BMI disutility. Additional multivariate analyses conducted during the evaluation indicated that the results were highly sensitive to the interaction between delay to insulin use, change in weight and hypoglycaemia event rates. The incremental cost per QALY for these plausible scenarios ranged from $15,000 - $45,000 to $105,000 - $200,000.

6.91 The results of the sensitivity analyses indicated that the comparison of semaglutide 0.5 mg versus dulaglutide once weekly was most sensitive to time horizon, baseline HbA1c, HbA1c drift, change in HbA1c with semaglutide treatment, hypoglycaemic event rates and costs. Additional multivariate analyses conducted during the evaluation indicated that the results were highly sensitive to the interaction between delay to insulin use, change in weight and hypoglycaemia event rates. The incremental cost per QALY for these plausible scenarios ranged from $15,000 - $45,000 to $45,000 - $75,000.

6.92 The results of the sensitivity analyses indicated that the comparison of semaglutide 1.0 mg versus dulaglutide once weekly was most sensitive to time horizon, hypoglycaemia event rates and costs, insulin disutility and BMI disutility. Additional multivariate analyses conducted during the evaluation indicated that the results were highly sensitive to the interaction between delay to insulin use, change in weight and hypoglycaemia event rates. The incremental cost per QALY for these plausible scenarios ranged from less than $15,000 to $15,000 - $45,000.

Drug cost/patient/year

6.93 The submission proposed a flat pricing structure for both dose strengths of semaglutide (0.5 mg and 1.0 mg). The estimated drug cost for semaglutide per patient per year was $[redacted] (based on published DPMQ per script $[redacted] / 28 days per script x 365 day per year).

6.94 The estimated drug cost for exenatide once weekly per patient per year was $1,710 (based on published DPMQ per script $131.15 / 28 days per script x 365 day per year).

6.95 The estimated drug cost for dulaglutide once weekly per patient per year was $1,710 (based on published DPMQ per script $131.15 / 28 days per script x 365 day per year).

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

Estimated PBS usage & financial implications

6.96 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and financial impact of listing semaglutide on the PBS/RPBS as part of dual/triple therapy for type 2 diabetes.

6.97 The estimated budget impact was based on published PBS prices. The submission acknowledged that exenatide once weekly and dulaglutide once weekly are subject to

Special Pricing Arrangements and therefore the published prices will overestimate the costs of these drugs.

6.98 The submission only provided 5 years of estimates due to the high degree of uncertainty associated with the GLP-1 market. The submission noted that updated estimates, including a six year forecast, could be provided closer to the time of listing should the PBAC make a positive recommendation. Crude sixth year estimates were calculated during the evaluation based on the data and assumptions used in the submission.

Table 17: Estimated use and financial implications

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)[a]
Exenatide 5mcg twice daily scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	10%	10%	10%	10%	10%	10%
Semaglutide scripts (1.07 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exenatide 10mcg twice daily scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	10%	10%	10%	10%	10%	10%
Semaglutide scripts (1.07 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exenatide once weekly scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	10%	25%	50%	50%	50%	50%
Semaglutide scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dulaglutide once weekly scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	10%	25%	50%	50%	50%	50%
Semaglutide scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitagliptin (all doses) scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	1%	2%	3%	4%	5%	6%
Semaglutide scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empagliflozin (all doses) scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	1%	2%	3%	4%	5%	6%
Semaglutide scripts (1.07 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insulin glargine scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Semaglutide substitution rate	0%	0%	0%	6%	12%	12%
Semaglutide scripts (6.70 adjustment factor)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total semaglutide scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Published cost of semaglutide scripts ($147.58)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient co-payments ($15.13 per script)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total cost less co-payment	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Cost offsets for substituted exenatide 5mcg twice daily	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted exenatide 10mcg twice daily	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted exenatide once weekly	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted dulaglutide once weekly	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted sitagliptin (all doses)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted empagliflozin (all doses)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offsets for substituted insulin glargine	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS[b]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

Source: Table 4-3 (p 204), Table 4-4 (p 206), Table 4-6 (p 209), Table 4-7 (p 210), Table 4-8 (p 211), Table 4-9 (p 212), Table 4-10 (p 212) of the submission

Abbreviations: DPMQ, dispensed price per maximum quantity; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

Note: Cost offsets based on published DPMQ minus average patient co-payment

[a] Calculated during the evaluation based on following assumptions; exenatide 5mcg twice daily 0% growth, 10% substitution; exenatide 10mcg twice daily 0% growth, 10% substitution; exenatide once weekly 0% growth, 50% substitution; exenatide once weekly 0% growth (based on trend), 50% substitution; sitagliptin (all dose strengths) 0% growth, 6% substitution (based on trend); empagliflozin 5% growth, 6% substitution (based on trend), insulin glargine 0% growth, 12% substitution (assumed same as previous year, basis for estimate unclear)

[b] The net cost to the PBS/RPBS was incorrectly estimated in the submission as the budget impact estimates did not include the cost offsets for sitagliptin and empagliflozin. These offsets were included during the evaluation.

The redacted table shows that at Year 6, the estimated number of semaglutide scripts was over 200,000.

6.99 The net cost of listing semaglutide for dual/triple therapy was estimated to be up to $30 - $60 million in the fifth year of listing (sixth year $30 - $60 million). The estimated cumulative net cost over five years was $60 - $100 million (cumulative cost over six years of more than $100 million).

6.100 The utilisation/financial estimates for semaglutide as dual/triple therapy were highly uncertain due to the following issues:

- The submission used sitagliptin and empagliflozin as proxies for the DPP4 and SGLT2 inhibitor markets respectively. There was no justification provided as to why these drugs were selected to represent all SGLT2 and DPP4 inhibitor use. The approach in the submission does not account for the substantial number of scripts attributable to other members of each class, fixed dose combinations with metformin and DPP4/SGLT2 inhibitor fixed dose combinations. The size and projected growth of these markets were substantially underestimated.
- The submission acknowledged that the GLP-1 market dynamics are highly uncertain:
    - The PBS script data used to predict the growth of dulaglutide was based on limited data, which was not adjusted for the PBS listing date that was halfway through 2018 (June to December 2018 estimates only). Updated script estimates to May 2019 suggest that dulaglutide utilisation will potentially be larger than exenatide once weekly by 2020, which is earlier than predicted in the submission;
    - The data suggest that the uptake of dulaglutide is being drawn from the broader diabetes market, outside of the GLP-1 market previously dominated by exenatide. There is a high risk of a similar trend occurring should semaglutide be listed on the PBS, particularly given its clinical claims of greater reduction in both HbA1c and body weight compared to other GLP-1 therapies;
    - In the first year of listing, there were 100,000 – 200,000 scripts for dulaglutide (June 2018 to May 2019) which is much larger than estimated for semaglutide of 50,000 – 100,000;
    - The submission assumed that 100% of exenatide twice daily market is for dual/triple therapy, however it likely that a substantial proportion of current

use is for combination with insulin. The implications of this assumption is unclear;

- The potential introduction of an oral formulation of semaglutide is likely to be highly disruptive to the GLP-1 market and the broader diabetes market.

- Cost-offsets due to substitution of insulin glargine were more likely to be delayed costs rather than true offsets as insulin may still be used with disease progression. Additionally, the estimates were based on highly uncertain assumptions surrounding HbA1c and delay in insulin use in the economic model (baseline HbA1c, treatment effect, magnitude of HbA1c drift and treatment thresholds). In many plausible scenarios the delay could occur after the projected financial estimates window.

- Substitution rates used to estimate cost offsets were assumed with no explanatory rationale provided in the submission. The ESC considered that the rates of substitution were not justified and that the actual rates of substitution could be much higher if substitution patterns increased within plausible bounds.

6.101 The ESC considered the estimated cost of listing semaglutide on the PBS was associated with significant uncertainties due to a substantially underestimated size and projected growth of the DPP4/SGLT2 inhibitor market, highly uncertain GLP-1 market dynamics, cost-offsets attributed to delay in insulin use and assumed substitution rates used to estimate cost-offsets.

6.102 The PBAC noted the net cost to the PBS would reduce from that proposed in the submission, once the effective price of exenatide and dulaglutide is applied and the semaglutide price is reduced based on a cost-minimisation to dulaglutide.

Quality Use of Medicines

6.103 The draft product information and additional post-market surveillance safety data include special warnings and precautions with semaglutide (injectable) due to its safety profile, particularly surrounding the management of gastrointestinal adverse events and diabetic retinopathy:

- Fixed dose escalation is recommended to improve gastrointestinal tolerability when initiating semaglutide treatment;

- Gastrointestinal effects may cause dehydration, which could cause a deterioration of renal function; and this should be considered in patients with impaired renal function;

- Gastrointestinal effects such as nausea, vomiting and diarrhoea may impact treatment compliance;

- Temporary worsening of diabetic retinopathy is a known adverse event associated with rapid blood glucose reduction, particularly during treatment initiation/titration. Patients may require additional monitoring during treatment

initiation/titration and any detected changes in the retina should be appropriately managed in order to prevent further complications.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of semaglutide (injectable) for treatment of patients with type 2 diabetes who have inadequate glycaemic control, as dual therapy in combination with metformin or a sulfonylurea where either of these is contraindicated or not tolerated; or triple therapy in combination with metformin and a sulfonylurea.

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of semaglutide would be acceptable if it were cost-minimised against dulaglutide.

7.3 The PBAC recommended semaglutide be listed as an Authority Required (STREAMLINED) benefit with a maximum quantity of 1 pen device and 5 repeats.

7.4 The PBAC advised that both exenatide and dulaglutide should be considered comparators to semaglutide.

7.5 The PBAC noted the proposed MCIDs for HbA1c and weight loss in the submission but considered the clinical importance of the nominated MCIDs was unclear. The PBAC considered a 0.5% reduction in HbA1c as suggested by the ESC was more relevant than the 0.3% proposed by the submission for a superiority claim. This outcome was met for semaglutide 1.0 mg in the comparison with exenatide 2.0 mg in the SUSTAIN 3 trial, but was not met in the comparison with dulaglutide 1.5 mg in SUSTAIN 7. However, in the context of the changing treatment algorithms based on patient-centred outcomes (see section 4 above), the clinical relevance of this surrogate outcome may shift.

7.6 The PBAC considered the weight loss outcomes from the SUSTAIN trials in the context of how significant weight loss was specified in the regulatory draft guidance from the FDA (see paragraph 6.12). The PBAC noted that when using this suggested MCID for weight loss, in the comparisons against both exenatide 2.0 mg and dulaglutide 1.5 mg, semaglutide 1.0 mg provided a meaningful difference in the proportion of patients achieving ≥ 5% weight loss by study end (56 weeks in SUSATIN 3 and 40 weeks in SUSTAIN 7). However, the sustainability of this weight loss and its translation into long-term clinical benefits remains unclear.

7.7 The PBAC considered that the baseline HbA1c and weight of the clinical trial populations were greater than the Australian population presenting in general practice and that the results expected from treatment may therefore be lower than seen in the SUSTAIN trials.

7.8 The PBAC noted the inclusion of the cardiovascular outcomes trial SUSTAIN 6. The PBAC noted that treatment with semaglutide (0.5 mg or 1.0 mg) was not associated with an increased risk of cardiovascular events compared with placebo based on the 3 point MACE outcome (HR 0.74; 95% CI 0.58, 0.95; p < 0.001 for non-inferiority). The PBAC considered the interpretation of the positive results was limited due to: the results being primarily driven by a decrease in the risk of non-fatal stroke and non-fatal myocardial infarction (no difference in cardiovascular deaths); testing for superiority for the primary outcome was conducted post-hoc and not adjusted for multiplicity; and median duration of follow-up was only 2.1 years.

7.9 The PBAC noted an increased risk of diabetic retinopathy complications compared with placebo in the SUSTAIN 6 trial (HR 1.76, 95% CI 1.11, 2.78). It was also noted there were higher rates of gastrointestinal adverse events for semaglutide 1.0 mg compared to exenatide 2.0 mg. However, on balance it was considered that the claim of non-inferior safety was reasonable for semaglutide 1.0 mg compared to both exenatide 2.0 mg and dulaglutide 1.5 mg noting that there may be an increased number of gastrointestinal events with semaglutide 1.0 mg compared to exenatide 2.0 mg.

7.10 Under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The PBAC considered that there was insufficient evidence to accept a superiority claim for semaglutide over dulaglutide and that there was low certainty in the modelled benefits over both exenatide and dulaglutide. The PBAC therefore recommended semaglutide on the basis of non-inferiority to dulaglutide.

7.11 The PBAC noted that the effects of semaglutide compared to dulaglutide 1.5 mg are attenuated if not titrated to the maximum dose (1.0 mg). The PBAC considered that this was an important consideration due to the high gastrointestinal side effect profile of semaglutide 1.0 mg and that it was probable that a substantial number of patients will use semaglutide 0.5 mg in preference to the 1.0 mg strength due to the relatively high response rates to HbA1c and weight loss targets. The PBAC noted the availability of semaglutide in overseas markets could have provided some information on the proportion of use of the 0.5 mg versus 1 mg strength in clinical practice.

7.12 The cost-utility analysis presented by the submission was not accepted given the clinical claim of superiority was not adequately supported. The PBAC noted the issues raised by the ESC and the evaluation with respect to the uncertainty in the drivers including disutilities due to insulin use, weight change and hypoglycaemia (see Table 13 above).

7.13 The Pre-PBAC Response stated that if the PBAC did not support the cost-utility approach, alternative recognition in the form of a price advantage, reflecting the mix of clinically relevant benefits in terms of HbA1c over exenatide and weight loss over

both comparators, with different but comparable safety, would be appropriate. The PBAC did not accept that a price premium was warranted given superiority was not accepted and the sustainability and clinical meaning of any initial benefit in weight loss was uncertain.

7.14 The recommended equi-effective doses for the cost-minimisation to dulaglutide are as follows: when used in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy) semaglutide 1.0 mg once weekly is equi-effective to dulaglutide 1.5 mg once weekly.

7.15 The PBAC did not consider that the proposal for the same price for both presentations of semaglutide was supported and pricing of the 0.5 mg dose of semaglutide would be determined by the Department according to usual methods.

7.16 The PBAC considered that the estimated cost of listing semaglutide on the PBS was associated with significant uncertainties due to a substantially underestimated size and projected growth of the DPP4/SGLT2 inhibitor market, highly uncertain GLP-1 market dynamics, cost-offsets attributed to delay in insulin use and assumed substitution rates used to estimate cost-offsets. With the cost per patient of semaglutide 1.0 mg the same as dulaglutide 1.5 mg, the overall financial impact will be closer to nil.

7.17 The PBAC considered that the management for type 2 diabetes has become increasingly complex due to the large number of medications available and changing treatment guidelines overseas. The PBAC noted that new Australian guidelines for the management of type 2 diabetes are due to be published in 2020 and are likely to be similar to the ADA/EASD guidelines. The PBAC considered that it may be appropriate to review the listings of medicines for type 2 diabetes once the guidelines are updated.

7.18 The PBAC advised that semaglutide should be treated as interchangeable on an individual patient basis with dulaglutide and exenatide.

7.19 The PBAC advised that semaglutide is suitable for prescribing by nurse practitioners.

7.20 The PBAC recommended that the Early Supply Rule should not apply.

7.21 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because semaglutide is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over dulaglutide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

7.22 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SEMAGLUTIDE			Ozempic®	Novo Nordisk
1.34 mg/1 mL injection, 1 x 1.5 mL pen device	1	5		
1.34 mg/1 mL injection, 1 x 3 mL pen device	1	5	Ozempic®	Novo Nordisk

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	The treatment must be in combination with metformin; OR The treatment must be in combination with a sulfonylurea, AND Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR Patient must not have tolerated a combination of metformin and a sulfonylurea, AND Patient must have, or have had, a 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 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.

Prescriber Instructions:	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. 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.
Administrative Advice:	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor. Special Pricing Arrangements Apply [TBC]

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	The treatment must be in combination with metformin, AND The treatment must be in combination with a sulfonylurea, AND Patient must have, or have had, a 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 maximally tolerated doses of metformin and a sulfonylurea; OR 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 maximally tolerated doses of metformin and a sulfonylurea.

Prescriber Instructions:	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. 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. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. 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.
Administrative Advice:	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin or an SGLT2 inhibitor. Special Pricing Arrangements Apply [TBC]

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.