6.10 SEMAGLUTIDE, Solution for injection 2 mg in 1.5 mL pre-filled pen, Solution for injection 4 mg in 3 mL pre-filled pen, Ozempic®, Novo Nordisk Pharmaceuticals Pty Ltd

1 Purpose of submission

1.1 The submission requested a Section 85, Authority Required (STREAMLINED) listing for semaglutide once weekly for the treatment of Type 2 Diabetes Mellitus (T2DM) in combination with insulin and metformin unless contraindicated or not tolerated.

1.2 The requested listing was based on a cost-minimisation analysis against dulaglutide 1.5 mg once weekly.

1.3 The submission positioned semaglutide, a glucagon like peptide 1 receptor agonist (GLP-1 RA), as an alternative to other GLP-1 RAs including dulaglutide (once weekly) and exenatide (twice daily) for use in combination with insulin and metformin (unless contraindicated or not tolerated) to treat T2DM in patients with inadequate glycaemic control despite treatment with insulin (and metformin).

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

Component	Description
Population	Patients with inadequately controlled T2DM on insulin (and metformin, unless not tolerated or contraindicated)
Intervention	Once titrated, semaglutide 0.5 mg or 1.0 mg once weekly
Comparator	Main comparator: dulaglutide 1.5 mg once weekly Secondary comparator: exenatide 5 mcg to 10 mcg twice daily Near-market comparator: lixisenatide with insulin glargine FRC administered once daily.
Outcomes	Glycaemic control (change from baseline in HbA1c), change from baseline in body weight, hypoglycaemic events, other safety outcomes (treatment emergent / serious adverse events).
Clinical claim	Semaglutide is non-inferior in effectiveness (change in HbA1c) and non-inferior in terms of safety (adverse events) compared with dulaglutide, exenatide and lixisenatide.

Source: Table 1.1.1, p14 of the submission.
Abbreviations: FRC, fixed ratio combination; HbA1c, glycated haemoglobin; T2DM, Type 2 Diabetes Mellitus

2 Background

Registration status

2.1 Semaglutide was TGA registered on 28 August 2019 for treatment of adults with insufficiently controlled T2DM 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 T2DM.

Previous PBAC consideration

2.2 The PBAC recommended semaglutide at its November 2019 meeting for treatment of patients with T2DM as dual therapy in combination with metformin or a sulfonylurea, and triple therapy in combination with metformin and a sulfonylurea.

2.3 In March 2020, the PBAC 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), both semaglutide 0.5 mg once weekly and 1.0 mg once weekly are equi-effective to dulaglutide 1.5 mg once weekly. The PBAC considered flat pricing across the semaglutide doses was acceptable based on the acceptance of a non-inferior outcome for both doses.

Current situation

2.4 Semaglutide was PBS-listed for use in dual/ triple therapy with metformin and/or a sulfonylurea on 1 July 2020.

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

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
SEMAGLUTIDE					
1.34 mg/1 mL injection, 1 x 1.5 mL pen device	1	5	$132.83	Ozempic®	Novo Nordisk Pharmaceuticals
1.34 mg/1 mL injection, 1 x 3 mL pen device	1	5	$132.83		

Restriction Summary 5469 / Treatment of Concept: 5469	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners
	Restriction type: ☒Authority Required – Streamlined [5469]
	Indication: Diabetes mellitus type 2
	Clinical criteria:
	The treatment must be in combination with insulin
	AND
	Clinical criteria:
	The treatment must be in combination with metformin unless contraindicated or not tolerated
	AND
	Clinical criteria:
	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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
	Prescribing 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.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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), or an SGLT2 inhibitor.
	Administrative Advice: *Special Pricing Arrangements apply.*

3.2 The sponsor proposed a Special Pricing Arrangement (SPA) for this indication, and suggested it could be achieved via a variation of the existing Deed of Agreement for semaglutide used in dual/triple therapy with metformin and/or a sulfonylurea. The submission did not propose an effective price for the requested indication with insulin and metformin unless contraindicated or not tolerated, stating that the sponsor was

awaiting PBS listing for dulaglutide in this indication. The PBAC noted that, as of 1 March 2021, dulaglutide once weekly (with or without metformin) can be co-prescribed with insulin on the PBS.

3.3 The requested restriction is narrower than the approved TGA indication as semaglutide must be used with insulin in combination with metformin (unless contraindicated or not tolerated), and patients must meet qualifying HbA1c or blood glucose levels.

3.4 The PBAC noted that the requested restriction for use of semaglutide with insulin and metformin (unless contraindicated or not tolerated) is consistent with the PBS listings of exenatide 5 mcg and 10 mcg twice daily, and dulaglutide once weekly. The pre-PBAC response acknowledged that the clinical criterion, "The treatment must be in combination with metformin unless contraindicated or not tolerated", was inadvertently omitted from the requested listing.

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

4 Population and disease

4.1 T2DM 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 Islander people 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 PBAC noted that in most clinical situations (endorsed by groups such as the Australian Diabetes Society and the American Diabetes Association), either SGLT2 inhibitors or GLP-1 RAs are now recommended as the next step in T2DM management when lifestyle changes and maximally tolerated metformin are insufficient to meet HbA1c targets[1]. The choice of either a GLP-1 RA or SGLT2 inhibitor is dependent upon the presence of cardiovascular disease, heart failure or kidney disease, or the need to minimise weight gain or promote weight loss; insulin can then be added if required. The PBAC also noted the submission's clinical management algorithm for T2DM from

[1] Diabetes Care 2018; 41(12): 2669-2701; https://care.diabetesjournals.org/content/41/12/2669

the Australian Diabetes Society, where a GLP-1 RA with insulin regimen is recommended as second-line and third-line treatment (with metformin as first-line therapy unless contraindicated or not tolerated)[2]. The PBAC considered that the requested listing provides for an additional option for GLP-1 RA treatment alongside the current PBS-listed regimens.

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

5 Comparator

5.1 The submission nominated dulaglutide 1.5 mg once weekly as the main comparator, as it is a GLP-1 RA with the same method and frequency of administration as semaglutide, and it received a positive recommendation by the PBAC in July 2020 for use in combination with insulin and metformin unless contraindicated or not tolerated on a cost-minimisation basis compared with exenatide 10 mcg BID. At the time of evaluation, dulaglutide had not yet been PBS-listed for this indication. The submission also nominated exenatide twice daily as a secondary comparator as it was the only GLP-1 RA listed on the PBS for the treatment of T2DM in combination with insulin at the time. The PBAC considered that these were appropriate comparators.

5.2 The submission also nominated once-daily lixisenatide (a GLP-1 RA) with insulin glargine fixed ratio combination (FRC) as a near market comparator, as it was considered (but not recommended) by the PBAC in March 2018 and March 2019. The evaluation considered that lixisenatide with insulin glargine was an appropriate potential comparator. However, the PBAC noted there have been no further considerations of lixisenatide with insulin glargine since the March 2019 PBAC meeting and did not consider it to be a relevant comparator for this submission.

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 (15) and organisations (2) via the Consumer Comments facility on the PBS website. The comments were all positive and described a range of benefits of treatment with semaglutide in combination with insulin including a higher proportion of patients achieving glucose targets compared to insulin and metformin alone, a reduction in the total daily dose of insulin required to achieve adequate glycaemic control (thereby

[2] ADS (2020). Australian Type 2 diabetes management algorithm. S. Australian Diabetes: 1-2.

reducing the risk of weight gain and hypoglycaemia associated with insulin), promotion of weight loss and cardiovascular protection, and improved quality of life.

Clinical trials

6.3 The submission was based on three separate indirect comparisons of one semaglutide trial (SUSTAIN 5) with: one dulaglutide trial (AWARD-9), one exenatide twice daily trial (GWCO) and one lixisenatide with insulin glargine trial (LIXILAN-L), with placebo/insulin glargine as common reference (LIXILAN-L was not further considered by PBAC for this submission). The SUSTAIN 5, AWARD-9 and GWCO trials were all placebo-controlled trials, with all participants also receiving basal insulin. Across all trials, between 81% and 90% of patients in each treatment arm were also receiving concomitant metformin.

6.4 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 5	SUSTAIN 5 – Add on to Basal Insulin: Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes Trial Phase: 3a. ClinicalTrials.gov Identifier: NCT02305381	June 2016
	Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): A randomized, controlled trial.	*J Clin Endocrin Metab* 2018; 103(6): 2291-2301.
	Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials.	*Diabetes Obes Metab* 2018; 20(9): 2210-2219.
	Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials.	*Diabetes Metab* 2019; 45(5): 409-418.
	De Souza C, Cariou B, Garg S, et al. Efficacy and safety of semaglutide for type 2 diabetes by race and ethnicity: a post hoc analysis of the SUSTAIN trials.	*J Clin Endocrin Metab* 2020; 105(2): 543-556.
	DeVries JH, De Souza C, Bellary, S, et al. Achieving glycaemic control without weight gain, hypoglycaemia, or gastrointestinal adverse events in type 2 diabetes in the SUSTAIN clinical trial programme.	*Diabetes Obes Metab* 2018; 20(10): 2426-2434.
	Jendle J, Birkenfeld AL, Polonsky WH, et al. Improved treatment satisfaction in patients with type 2 diabetes treated with once-weekly semaglutide in the SUSTAIN trials.	*Diabetes Obes Metab* 2019; 21(10): 2315-2326.
	Rodbard HW, Bellary S, Hramiak I, et al. Greater combined reductions in HbA1c ≥1.0% and weight ≥5.0% with semaglutide versus comparators in type 2 diabetes.	*Endocrine Practice* 2019; 25(6): 589-597.
AWARD-9	Pozzilli P, Norwood P, Jodar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9).	*Diabetes Obes Metab* 2017; 19(7): 1024-1031.
	Yu M, Van Brunt K, Milicevic Z, et al. Patient-reported Outcomes in Patients with Type 2 Diabetes Treated with Dulaglutide Added to Titrated Insulin Glargine (AWARD-9).	*Clinical Therapeutics* 2017; 39(11): 2284-2295.
GWCO	Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes.	*Ann Int Med* 2011; 154(2): 103-112.

Trial ID	Protocol title/ Publication title	Publication citation
	Buse JB, Han J, Miller S, et al. Addition of exenatide BID to insulin glargine: A post-hoc analysis of the effect on glycemia and weight across a range of insulin titration.	*Current Medical Research and Opinion* 2014; 30(7): 1209-1218.
	Rosenstock J, Shenouda SK, Bergenstal RM, et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes.	*Diabetes Care* 2012; 35(5): 955-958.
LIXILAN-L	Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes not adequately controlled on basal insulin: LixiLan-L trial.	*Diabetologia* 2016b; 59(1): S2-S3.
	Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: The LixiLan-L randomized trial.	*Diabetes Care* 2016; 39(11): 1972-1980.
	Blonde L, Bailey TS, Chao J, et al. Clinical characteristics and glycemic outcomes of patients with type 2 diabetes requiring maximum dose insulin glargine/lixisenatide fixed-ratio combination or insulin glargine in the LixiLan-L trial.	*Adv Ther* 2019; 36(9): 2310-2326.
	Blonde L, Berard L, Saremi A, et al. Fixed-Ratio Combination of Insulin and GLP-1 RA in Patients with Longstanding Type 2 Diabetes: A Subanalysis of LixiLan-L.	*Diabetes Ther* 2020; 11(4): 1007-1015.
	Dailey G, Bajaj HS, Dex T, et al. Post hoc efficacy and safety analysis of insulin glargine/lixisenatide fixed- ratio combination in North American patients compared with the rest of world.	*BMJ Open Diab Res Care* 2019; 7(1):e000581
	Davidson JA, Desouza C, Fonseka V, et al. Glycaemic target attainment in people with Type 2 diabetes treated with insulin glargine/lixisenatide fixed-ratio combination: a post hoc analysis of the LixiLan-O and LixiLan-L trials.	*Diabet Med* 2020; 37(2):256-266.
	Handelsman Y, Chovanes C, Dex T, et al. Efficacy and safety of insulin glargine/lixisenatide (iGlarLixi) fixed-ratio combination in older adults with type 2 diabetes.	*J Diabetes Complications* 2019; 33(3): 236-242.
	Morea N, Retnakaran R, Vidal J, et al. iGlarLixi effectively reduces residual hyperglycaemia in patients with type 2 diabetes on basal insulin: A post hoc analysis from the LixiLan-L study.	*Diabetes Obes Metab* 2020; 22(9): 1683-1689.
	Niemoeller E, Souhami E, Wu Y, Jensen KH. iGlarLixi reduces glycated hemoglobin to a greater extent than basal insulin regardless of levels at screening: Post hoc analysis of LixiLan-L.	*Diabetes Ther* 2018; 9(1): 373-382.
	Wysham C, Bonadonna RC, Aroda, VR, et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) versus insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial.	*Diabetes Obes Metab* 2017; 19(10): 1408-1415.
	Zisman A, Dex T, Roberts M, et al. Bedtime-to-morning glucose difference and iGlarLixi in type 2 diabetes: Post hoc analysis of LixiLan-L.	*Diabetes Ther* 2018; 9(5): 2155-2162.

Source: Table 2.2.3, pp35-38 of the submission.
Note: Abstracts of studies with full publications are not presented.

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

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Semaglutide vs placebo (with concomitant basal insulin)					
SUSTAIN 5	397	Phase 3, multi-centre, double blind, placebo-controlled, parallel group RCT (30 weeks)	Low	Type 2 diabetes with uncontrolled HbA1c on basal insulin (with or without metformin)	Change from baseline in HbA1c, FPG, body weight; HbA1c responders, hypoglycaemia
Dulaglutide vs placebo (with concomitant insulin glargine)					
AWARD-9	300	Phase 3, multi-centre, double blind, placebo-controlled, parallel group RCT (28 weeks)	Low	Type 2 diabetes with uncontrolled HbA1c on basal insulin (with or without metformin)	Change from baseline in HbA1c, FSG, body weight; HbA1c responders, hypoglycaemia
Exenatide vs placebo (with concomitant insulin glargine)					
GWCO	261	Phase 3, double blind, placebo-controlled, parallel group RCT (30 weeks)	Low	Type 2 diabetes with uncontrolled HbA1c on basal insulin (with or without metformin and/or pioglitazone)	Change from baseline in HbA1c, FPG, body weight; HbA1c responders, hypoglycaemia

Source: Compiled from information presented in Sections 2.3 and 2.4, pp39-57 of the submission.
Abbreviations: FPG, fasting plasma glucose; FSG, fasting serum glucose; HbA1c, glycated haemoglobin; RCT, randomised controlled trial.

6.6 The trials were generally comparable in terms of the enrolled population. However, there were differences in study design, particularly the insulin titration algorithms. In the SUSTAIN 5, AWARD-9 and GWCO trials, patients with HbA1c ≤8.0% at randomisation immediately decreased their insulin dose by 20% to limit the potential risk of hypoglycaemia. The PBAC noted that down-titration (apart from the initial 20% reduction in dose) was only permitted in SUSTAIN 5 for 12 weeks (weeks 0-12) and AWARD-9 for 24 weeks (week 5-28). Down-titration of insulin was also permitted for rescue therapy.

6.7 In SUSTAIN 5, up-titration of basal insulin dose was only permitted for patients with HbA1c ≤8.0% at baseline, and only between weeks 10 and 16 (7 weeks), and insulin dose was not to exceed the pre-randomisation dose. In contrast, up-titration was permitted after an initial stabilisation period for the remainder of the trial for all patients in the AWARD-9 (week 5-28, 24 weeks) and GWCO (week 6-30, 25 weeks), with no upper limit.

6.8 The difference in insulin titration algorithms between SUSTAIN 5 and the comparator trials may limit the exchangeability of the trials for indirect analysis.

6.9 In the SUSTAIN 5 trial, there were two placebo arms that received different volumes of placebo to match the injection volumes for the two semaglutide dose strengths, but the placebo arms were pooled for the assessment of comparative efficacy and safety. The SUSTAIN 5 Clinical Study Report noted no association between the volume of placebo administered and HbA1c or body weight outcomes, which was appropriate.

Comparative effectiveness

Semaglutide + insulin versus placebo + insulin

6.10 The SUSTAIN 5 trial used a subset of the full analysis set, labelled as 'on-treatment without rescue medication' when reporting efficacy outcomes. The observation period for this dataset censored for premature treatment discontinuations as well as use of anti-diabetic rescue medications, to avoid confounding of efficacy outcomes from rescue medication use. The PBAC noted that basal insulin dose increase was the first choice for rescue medication and was required in only 6% of the 397 randomised patients (3 (2.3%) patients from the semaglutide 0.5 mg group, 1 patient (0.8%) in the semaglutide 1.0 mg group, and 19 (14.3%) patients in the placebo group). 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, but the difference between treatments was smaller.

6.11 Key outcomes for change in HbA1c from the SUSTAIN 5 trial are presented in the table below.

Table 4: Change in HbA1c (%) and proportions of patients achieving HbA1c targets of < 7.0% or ≤ 6.5% from baseline to week 30 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 30, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference versus placebo (95% CI)[a]
Change in HbA1c (%) from baseline to week 30 [primary outcome]					
Sema 0.5 mg	132	8.36 (0.83)	6.92 (0.09)	-1.45 (0.09)	**-1.35 (-1.61, -1.10)**
Sema 1.0 mg	131	8.31 (0.82)	6.52 (0.09)	-1.85 (0.09)	**-1.75 (-2.01, -1.50)**
Placebo	133	8.42 (0.88)	8.27 (0.09)	-0.09 (0.09)	-
Treatment arms	**N**	**Patients, n/N (%)**			**Odds ratio (95% CI)**
Proportion of subjects achieving an HbA1c target of < 7.0% at week 30 [secondary outcome]					
Sema 0.5 mg	132	80/132 (61)			**14.68 (7.43, 29.02)**
Sema 1.0 mg	131	103/131 (79)			**34.28 (16.59, 70.83)**
Placebo	133	14/133 (11)			-
Proportion of subjects achieving an HbA1c target of ≤ 6.5% at week 30 [secondary outcome]					
Sema 0.5 mg	132	54/132 (41)			**15.61 (6.47, 37.64)**
Sema 1.0 mg	131	80/131 (61)			**35.84 (14.72, 87.27)**
Placebo	133	6/133 (5)			-

Source: Table 2.5.1, p65; Table 2.5.3, Table 2.5.4, p67 of the submission.
Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; sema, semaglutide
[a] Estimated using a mixed model for repeated measures, with treatment, country and stratification variable (HbA1c level at screening [≤ 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit.

6.12 For the primary outcome (change from baseline to week 30 in HbA1c) from SUSTAIN 5, the PBAC noted there was a statistically significant mean treatment difference versus placebo (95% CI) of -1.35 (-1.61, -1.10) and -1.75 (-2.01, -1.50) for semaglutide 0.5 mg and semaglutide 1.0 mg respectively. The proportion of treatment responders was also statistically significantly greater in the semaglutide treatment arm compared with placebo. For the proportion of patients achieving an HbA1c target of < 7.0% at week 30 (a common goal in T2DM management), the PBAC noted that 79% and 61% of

patients achieved this target in the semaglutide 1.0 mg and 0.5 mg groups respectively, compared to 11% of patients in the placebo group. The study authors noted that the lack of insulin dose up- titration in the placebo arm may have been responsible for HbA1c levels remaining elevated in this arm (Rodbard 2018).

6.13 Treatment with both semaglutide 0.5 mg and 1.0 mg once weekly was also associated with a statistically significant reduction in both mean 7-point self-monitored plasma glucose and mean fasting plasma glucose from baseline to week 30 compared with placebo, in combination with basal insulin. Similar to the results for change in HbA1c in Table 4, the PBAC noted that, with respect to mean fasting plasma glucose, there was a statistically significant mean treatment difference versus placebo (95% CI) of -1.14 (-1.75, -0.54) for semaglutide 0.5 mg, and -1.88 (-2.48, -1.28) for semaglutide 1.0 mg.

6.14 Change in body weight from baseline to week 30 in the SUSTAIN 5 trial is presented in the table below.

Table 5: Change in bodyweight (kg) from baseline to week 30 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 30, mean (SE)[a]	Mean change (SE)[a]	Mean treatment difference versus placebo (95% CI)[a]
Change in body weight from baseline to week 30 [secondary outcome]					
Sema 0.5 mg	132	92.74 (19.57)	88.02 (0.36)	-3.67 (0.36)	**-2.31 (-3.33, -1.29)**
Sema 1.0 mg	131	92.49 (22.23)	85.27 (0.36)	-6.42 (0.36)	**-5.06 (-6.08, -4.04)**
Placebo	133	89.88 (21.06)	90.33 (0.37)	-1.36 (0.37)	-

Source: Table 2.5.2, p66 of the submission.

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; sema, semaglutide

[a] Estimated using a mixed model for repeated measures, with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit.

6.15 Treatment with both semaglutide 0.5 mg and 1.0 mg once weekly was associated with a statistically significant reduction in body weight from baseline to week 30 compared with placebo, in combination with basal insulin (a secondary outcome). The change in body weight was notably greater in the semaglutide 1.0 mg dose arm (-5.06; 95% CI: -6.08, -4.04) compared to the 0.5 mg dose (-2.31; 95% CI: -3.33, -1.29), and there was a small proportion (mean change -1.36 kg) who lost weight in the placebo arm. The PBAC noted there was another secondary outcome for patients achieving a weight loss target of $\geq$5%, and considered this to be another common goal in T2DM management; 66% and 42% of patients achieved this target in the semaglutide 1.0 mg and 0.5 mg groups respectively, compared to 11% of patients in the placebo group.

6.16 The table below summarises the change in mean basal insulin dose from baseline to week 30 in the SUSTAIN 5 trial.

Table 6: Change in basal insulin dose from baseline to week 30 (on treatment without rescue medication)

Treatment arms	N	Baseline, mean (SD)	Week 30, mean (SD)[a]	Mean change (SE)[a]	Mean treatment difference versus placebo (95% CI)[a]
Change in geometric mean basal insulin dose (U/day) from baseline to week 30 [secondary outcome]					
Sema 0.5 mg	132	39.30 (*0.68*)	35.45 (*0.63*)	*-3.85 (0.1)*	***-2.5 (-2.7, -2.2)***
Sema 1.0 mg	131	37.35 (*0.64*)	31.50 (*0.47*)	*-5.85 (0.1)*	***-4.5 (-4.3, -4.7)***
Placebo	133	36.64 (*0.65*)	35.25 (*0.60*)	*-1.39 (0.1)*	-

Source: Table 2.5.6, p69 of the submission.

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; sema, semaglutide; U, insulin units

[a] Estimated using a mixed model for repeated measures, with treatment, country and stratification variable (HbA1c level at screening [<= 8.0% or > 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit.

Numbers in italics were calculated for the submission. Calculations could not be found during the evaluation and could not be verified. The SUSTAIN 5 Clinical Study Report presented Ratio at week 30 compared to baseline, and compared the Treatment Ratio for semaglutide versus placebo. Results for this measure were also statistically significantly different in favour of semaglutide.

6.17 The reduction in mean daily basal insulin dose was statistically significantly greater in the semaglutide arm compared to the placebo arm. The submission stated that this was expected to be primarily caused by the insulin titration protocol used in the trial. The largest overall decrease in insulin dose was in patients with baseline HbA1c ≤8%, where patients reduced their insulin dose by 20% from randomisation as required by the study protocol. The difference between treatment groups for change in insulin dose in patients with HbA1c >8% was not as pronounced.

6.18 The submission also presented quality of life data comparing change in scores from baseline to week 30, from the 36-item Short Form health survey (SF-36v2), and the Diabetes Treatment Satisfaction Questionnaire (DTSQ). At week 30, most domains of the SF-36v2 showed improvement for all three treatment groups, but there were no statistically significant differences between either semaglutide 0.5mg or semaglutide 1.0 mg and placebo for the change from baseline to week 30. At week 30, all nine components of the DTSQ (including the 'treatment satisfaction' summary domain score) showed improvements for all three treatment groups. Three components plus the overall treatment satisfaction score showed statistically significantly greater improvement in the semaglutide 0.5 mg arm over placebo, and seven components plus the overall treatment satisfaction score showed statistically significantly greater improvements in the semaglutide 1.0 mg arm over placebo.

Indirect comparisons

6.19 The submission presented two separate indirect comparisons of semaglutide (either 0.5 mg or 1.0 mg) with dulaglutide 1.5 mg, and exenatide 10 mcg twice daily, with placebo as common reference, and with all treatments in combination with basal insulin. The submission used the Bucher single pairwise method for the indirect comparisons, which were based on the primary outcome for all trials (change from baseline in HbA1c) and secondary outcomes from SUSTAIN 5 that were also reported in the comparator studies (change from baseline in body weight, proportion achieving HbA1c targets, change in 7-point self-monitored plasma glucose profile, change in basal insulin dose, and safety outcomes). The submission's indirect comparison used the 'on treatment without rescue medication' analysis set from SUSTAIN 5, which

excluded observation periods beyond premature treatment discontinuation and after initiation of rescue medication.

6.20 The PBAC noted that the submission nominated a non-inferiority margin of 0.3% to 0.4%, whereby non-inferiority is demonstrated when the upper 95% confidence limit does not cross this boundary for the outcome of change from baseline in HbA1c, as used in the March 2018 lixisenatide submission (Para 7.6, lixisenatide with insulin glargine, Public Summary Document (PSD), March 2018 PBAC meeting), and the March 2015 exenatide twice daily submission (Para 6.7, exenatide, PSD, March 2015 PBAC meeting). Similarly, in the November 2019 dulaglutide submission (Para 6.16, dulaglutide, PSD, November 2019 PBAC meeting) a non-inferiority margin of 0.3% was nominated for change from baseline in HbA1c.

6.21 The submission noted that in the November 2019 consideration of semaglutide for dual/triple therapy with metformin and/or a sulfonylurea, the PBAC considered a 0.5% reduction in HbA1c to be more relevant than 0.3% for a superiority claim (Para 5.10, November 2019, semaglutide PSD). The PBAC noted that, while the current submission is based on a claim of non-inferiority, the results of the indirect comparisons were also assessed for superiority.

Indirect comparison of semaglutide and dulaglutide

6.22 Results of the indirect comparison of semaglutide and dulaglutide for the primary outcome of change from baseline in HbA1c are presented in the table below. The endpoint for SUSTAIN 5 was week 30, and for AWARD-9 was week 28.

Table 7: Indirect comparison of semaglutide and dulaglutide for change from baseline in HbA1c (%) at week 28/30

Trial	Change from baseline in HbA1c % LSM (SE)			LSM (95% CI)
	Semaglutide (30 weeks)	Placebo	Dulaglutide (28 weeks)	
Semaglutide 0.5 mg vs dulaglutide 1.5 mg				
SUSTAIN 5	-1.45 (0.09)	-0.09 (0.09)	-	-1.35 (-1.61, -1.10)
AWARD-9	-	-0.67 (0.09)	-1.44 (0.09)	-0.77 (-0.97, -0.56)
Indirect mean difference < 0 favours semaglutide				**-0.58 (-0.91, -0.25)**
Semaglutide 1.0 mg vs dulaglutide 1.5 mg				
SUSTAIN 5	-1.85 (0.09)	-0.09 (0.09)	-	-1.75 (-2.01, -1.50)
AWARD-9	-	-0.67 (0.09)	-1.44 (0.09)	-0.77 (-0.97, -0.56)
Indirect mean difference < 0 favours semaglutide				**-0.98 (-1.31, -0.65)**

Source: Table 2.6.2, p81; Table 2.6.3, p82 of the submission; Attachment 5 of the submission.
Abbreviations: CI, confidence interval; LSM, least square mean; SE, standard error; MD, mean difference; bold = statistically significant
Note: SE were calculated with the assumption of a normal distribution.

6.23 Both semaglutide treatment arms had a statistically significantly greater reduction from baseline in HbA1c compared to dulaglutide. The submission noted that the point estimates for the mean differences with both semaglutide doses exceeded 0.5%, which has previously been considered to be a potentially relevant minimal clinically important difference (MCID) for testing superiority. However, there were large differences in HbA1c outcomes across the placebo arms of the trials (HbA1c mean change from baseline -0.09% vs -0.67%), indicating that there may be differences between the trials that limit their exchangeability. Limiting the ability of patients in

the SUSTAIN 5 trial to titrate insulin doses, and excluding patients who required rescue medication from the analysis, appeared to result in poorer outcomes for patients in the placebo arm of the trial compared to the placebo arms from the comparator trials, which favours semaglutide.

6.24 An alternative indirect comparison between the 'in-trial' analysis set from SUSTAIN 5 (not censoring for rescue medication or premature treatment discontinuations, see Figure 11-3, p152 of the SUSTAIN 5 Clinical Study Report) and the dulaglutide ITT analysis for change from baseline in HbA1c was conducted during the evaluation. Results remained statistically significant in favour of semaglutide, however the magnitude of the difference was smaller (semaglutide 0.5 mg vs dulaglutide: -0.46, 95% CI -0.79, -0.13; semaglutide 1.0 mg vs dulaglutide: -0.83, 95% CI -1.16, -0.50).

6.25 Similarly, the indirect comparison of the proportion of patients reaching HbA1c targets of ≤6.5% or <7.0% suggested a statistically significant difference in favour of semaglutide 0.5 mg or 1.0 mg over dulaglutide. There were large differences in proportion of HbA1c responders in the placebo arms of the trials (proportion of placebo patients achieving HbA1c of ≤6.5% or <7.0% at endpoint was 4.5% and 10.5%, respectively, in the SUSTAIN 5 semaglutide trial, compared to 16.7% and 33.3%, respectively, in the AWARD-9 dulaglutide trial), which the PBAC considered may limit their exchangeability.

6.26 Results of the indirect comparison between semaglutide and dulaglutide for change from baseline in body weight (kg) at week 28/30 are presented in the table below.

Table 8: Indirect comparison of semaglutide and dulaglutide for change from baseline in body weight (kg) at week 28/30

Trial	Change from baseline in body weight, kg, LSM (SE)			LSM (95% CI)
	Semaglutide (30 weeks)	Placebo	Dulaglutide (28 weeks)	
Semaglutide 0.5 mg vs dulaglutide 1.5 mg				
SUSTAIN 5	-3.67 (0.36)	-1.36 (0.37)	-	-2.31 (-3.33, -1.29)
AWARD-9	-	0.7 (0.2)	-0.7 (0.2)	-2.41 (-3.19, -1.64)
Indirect mean difference < 0 favours semaglutide				0.10 (-1.18, 1.38)
Semaglutide 1.0 mg vs dulaglutide 1.5 mg				
SUSTAIN 5	-6.42 (0.36)	-1.36 (0.37)	-	-5.06 (-6.08, -4.04)
AWARD-9	-	0.7 (0.2)	-0.7 (0.2)	-2.41 (-3.19, -1.64)
Indirect mean difference < 0 favours semaglutide				**-2.65 (-3.93, -1.37)**

Source: Table 2.6.4, p82; Table 2.6.5, p83 of the submission; Attachment 5 of the submission.
Abbreviations: CI, confidence interval; LSM, least square mean; SE, standard error; MD, mean difference; bold = statistically significant
Note: SE were calculated with the assumption of a normal distribution.

6.27 Change from baseline in body weight was statistically significantly greater in the semaglutide 1.0 mg arm compared to dulaglutide, but not for semaglutide 0.5 mg versus dulaglutide. There were large differences in body weight change between the placebo groups of the trials (mean change in body weight from baseline -1.36 kg versus +0.7 kg).

Indirect comparison of semaglutide and exenatide

6.28 Results of the indirect comparison of semaglutide and exenatide for the primary outcome of change from baseline in HbA1c are presented in the table below.

Table 9: Indirect comparison of semaglutide and exenatide for change from baseline in HbA1c (%) at week 30

Trial	Change from baseline in HbA1c % LSM (SE)			LSM (95% CI)
	Semaglutide (30 weeks)	Placebo	Exenatide (30 weeks)	
Semaglutide 0.5 mg vs exenatide 10 mcg				
SUSTAIN 5	-1.45 (0.09)	-0.09 (0.09)	-	-1.35 (-1.61, -1.10)
GWCO	-	-1.04 (NR)	-1.74 (NR)	-0.69 (-0.93, -0.46)
Indirect mean difference < 0 favours semaglutide				**-0.66 (-1.00, -0.32)**
Semaglutide 1.0 mg vs exenatide 10 mcg				
SUSTAIN 5	-1.85 (0.09)	-0.09 (0.09)	-	-1.75 (-2.01, -1.50)
GWCO	-	-1.04 (NR)	-1.74 (NR)	-0.69 (-0.93, -0.46)
Indirect mean difference < 0 favours semaglutide				**-1.06 (-1.40, -0.72)**

Source: Table 2.6.2, p81; Table 2.6.3, p82 of the submission; Attachment 5 of the submission.
Abbreviations: CI, confidence interval; LSM, least square mean; SE, standard error; MD, mean difference; bold = statistically significant
Note: SE were calculated with the assumption of a normal distribution.

6.29 Both semaglutide treatment arms had a statistically significantly greater reduction from baseline in HbA1c at week 30 compared to exenatide. The submission noted that the point estimates for the mean differences with both semaglutide doses exceeded 0.5%, which has been previously considered to be a potentially relevant MCID for testing superiority. Similarly, a significantly greater proportion of patients receiving semaglutide 0.5 mg or 1.0 mg reached HbA1c targets of ≤6.5% or <7.0% (≤7.0% in the GWCO trial) compared with exenatide at week 30. However, the PBAC considered there were large differences in HbA1c outcomes across the placebo arms of the trials (mean change from baseline in HbA1c -0.09% versus -1.04%; HbA1c ≤6.5%: 4.5% vs 12.3%; HbA1c <7.0%: 10.5% versus 35.2%), indicating that there may be differences between the trials that limit their exchangeability.

6.30 An alternative indirect comparison between the 'in-trial' analysis set from SUSTAIN 5 (not censoring for rescue medication or premature treatment discontinuations, see Figure 11-3, p152 of the SUSTAIN 5 Clinical Study Report) and the exenatide ITT analysis for change from baseline in HbA1c was conducted during the evaluation. Results remained statistically significant in favour of semaglutide, however the magnitude of the difference was smaller (semaglutide 0.5 mg vs exenatide: -0.54, 95% CI -0.88, -0.20; semaglutide 1.0 mg vs exenatide: -0.91, 95% CI -1.25, -0.57).

6.31 The table below presents results of the indirect comparison between semaglutide and exenatide for change from baseline in body weight (kg) at week 30.

Table 10: Indirect comparison of semaglutide and exenatide for change from baseline in body weight at week 30

Trial	Change from baseline in body weight, kg, LSM (SE)			LSM (95% CI)
	Semaglutide (30 weeks)	Placebo	Exenatide (30 weeks)	
Semaglutide 0.5 mg vs exenatide 10 mcg				
SUSTAIN 5	-3.67 (0.36)	-1.36 (0.37)	-	-2.31 (-3.33, -1.29)
GWCO	-	0.96 (NR)	-1.78 (NR)	-2.74 (-3.74, -1.74)
Indirect mean difference < 0 favours semaglutide				0.43 (-1.00, 1.86)
Semaglutide 1.0 mg vs exenatide 10 mcg				
SUSTAIN 5	-6.42 (0.36)	-1.36 (0.37)		-5.06 (-6.08, -4.04)
GWCO	-	0.96 (NR)	-1.78 (NR)	-2.74 (-3.74, -1.74)
Indirect mean difference < 0 favours semaglutide				**-2.32 (-3.75, -0.89)**

Source: Table 2.6.4, p82; Table 2.6.5, p83 of the submission; Attachment 5 of the submission.
Abbreviations: CI, confidence interval; LSM, least square mean; SE, standard error; MD, mean difference; bold = statistically significant
Note: SE were calculated with the assumption of a normal distribution.

6.32 Change from baseline in body weight was statistically significantly greater in the semaglutide 1.0 mg arm compared to exenatide, but not for semaglutide 0.5 mg versus exenatide. There were large differences in change from baseline in body weight between placebo arms of the trials (mean change from baseline in body weight -1.36 kg versus +0.96 kg).

Comparative harms

6.33 Key adverse events from the SUSTAIN 5 trial are summarised in the table below.

Table 11: Summary of key adverse events in the SUSTAIN 5 trial (on-treatment without rescue medication analysis)

Adverse event of interest	Semaglutide 0.5 mg N=132, n (%)	Semaglutide 1.0 mg N=131, n (%)	Placebo N=133, n (%)
Any adverse event	91 (68.9)	84 (64.1)	77 (57.9)
Serious adverse event	8 (6.1)	12 (9.2)	9 (6.8)
Discontinuation due to adverse event	6 (4.5)	8 (6.1)	1 (0.8)
Deaths	0 (0)	0 (0)	0 (0)
Gastrointestinal adverse events	36 (27.3)	45 (34.4)	21 (15.8)
Nausea	15 (11.4)	22 (16.8)	6 (4.5)
Vomiting	8 (6.1)	15 (11.5)	4 (3.0)
Diarrhoea	6 (4.5)	9 (6.9)	2 (1.5)

Source: Table 2.5.7, p74; Table 2.5.8, Table 2.5.9, p75; Table 2.5.10, Table 2.5.11, p76 of the submission
Abbreviations: CI, confidence interval; GI, gastrointestinal; OR, odds ratio; RD, risk difference; RR, relative risk; Sema, semaglutide

6.34 There were no differences between treatment groups in the number of adverse events or serious adverse events, and no treatment related pattern was observed. The PBAC noted that gastrointestinal adverse events (a well-described side effect of GLP-1 RAs) were the most frequently reported adverse events with semaglutide, particularly nausea, vomiting and diarrhoea, all of which were reported at a higher rate and by a higher proportion of subjects with each of the semaglutide doses than with placebo. The PBAC considered there was only a small number of patients who discontinued in the active arms due to adverse events (4.5% and 6.1% for semaglutide 0.5 mg and 1.0 mg respectively).

6.35 The evaluation considered numbers of hypoglycaemic events using either the sponsor-defined "severe or blood glucose confirmed symptomatic episodes of hypoglycaemia", or the American Diabetes Association-defined hypoglycaemia categories. The PBAC noted that the rate of hypoglycaemic episodes was higher in the semaglutide arms of the SUSTAIN 5 trial compared to the placebo arm (particularly for patients commencing treatment with an HbA1c ≤8.0% and for those on the higher 1.0 mg dose), but the difference was not statistically significant. The rates of severe hypoglycaemic events in all treatment arms was very low and not statistically significantly different between the semaglutide and placebo arms of SUSTAIN 5.

6.36 The submission presented an indirect comparison of safety outcomes between semaglutide and each of the three comparators, including treatment emergent adverse events, serious adverse events, withdrawal due to an adverse event, and deaths. The PBAC noted there were no statistically significant differences between either dose strength of semaglutide and dulaglutide or exenatide for any of these outcomes.

6.37 Results of indirect comparisons of documented hypoglycaemic events suggest that patients treated with dulaglutide have statistically significantly fewer documented hypoglycaemic events than patients treated with semaglutide 0.5 mg (Event rate ratio [ERR] vs dulaglutide 1.28, 95% CI 1.05, 1.56) or 1.0 mg (ERR vs dulaglutide 1.74, 95% CI 1.40, 2.17). The submission suggested that this may be a result of trial design differences whereby patients in SUSTAIN 5 were more limited in their ability to up- or down-titrate insulin. Based on differences observed in the placebo groups of SUSTAIN 5 and the comparator trials (AWARD-9 and GWCO), the differences in trial design are also likely to impact the exchangeability of the trial results for the hypoglycaemia outcomes.

Clinical claim

6.38 The submission described semaglutide as non-inferior in terms of effectiveness compared to dulaglutide and exenatide twice daily. The evaluation considered that the therapeutic conclusion presented in the submission may be reasonable, but differences in placebo group outcomes suggest that the design of the SUSTAIN 5 trial, particularly the differences in insulin titration algorithms, may limit the exchangeability of these trials. Limiting the ability of patients in the SUSTAIN 5 trial to titrate insulin doses, and excluding patients who required rescue medication from the analysis, appeared to result in poorer outcomes for patients in the placebo arm of the trial compared to the placebo arms in the comparator trials, which favours semaglutide. The pre-PBAC response stated that using the alternative indirect comparisons conducted during the evaluation, i.e. not censoring for rescue medication or premature treatment discontinuations (see paragraphs 6.24 and 6.30), results for both semaglutide doses remained statistically significant in terms of a greater reduction in HbA1c compared with dulaglutide or exenatide, and that this justifies the exchangeability of the trials. The response also stated that, for the

purpose of the submission, a conservative claim of non-inferiority (rather than superiority) was made with respect to relative effectiveness.

6.39 The submission described semaglutide as non-inferior in terms of safety compared to dulaglutide and exenatide twice daily. The evaluation considered this claim was adequately supported. There was a statistically significant higher rate of documented hypoglycaemia events in patients treated with semaglutide 0.5 mg or 1.0 mg compared with dulaglutide, but this may have been a result of trial design differences, with SUSTAIN 5 participants more limited in their ability to up- or down-titrate basal insulin doses compared to the comparator trials.

6.40 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable and adequately supported by the available data.

Economic analysis

6.41 The submission presented a cost-minimisation analysis comparing semaglutide 0.5 mg or 1.0 mg with dulaglutide 1.5 mg. The equi-effective doses were estimated as semaglutide 0.5 or 1.0 mg once weekly and dulaglutide 1.5 mg once weekly. Treatment is ongoing. The equi-effective doses were trial-based and are the same as the current TGA-approved doses for each medicine, and the same as the current PBS-listed doses for each medicine in dual/triple therapy with metformin and/or a sulfonylurea.

6.42 The cost-minimisation analysis was conducted on a cost per week basis, and included drug costs only. Results of the cost-minimisation analysis are presented in the table below.

Table 12: Results of the cost-minimisation analysis

Component	Semaglutide 0.5 mg or 1.0 mg	Dulaglutide 1.5 mg
Cost per dose	$27.86 (AEMP) / $33.21 (DPMQ)	$27.86 (AEMP) / $33.21 (DPMQ)
Dose duration	1 week	1 week
Administrations per week	1	1
Total medicine cost per week	$27.86 (AEMP) / $33.21 (DPMQ)	$27.86 (AEMP) / $33.21 (DPMQ)

Source: Table 3.4.1, p104 of the submission.
Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price for maximum quantity.

6.43 Dulaglutide and semaglutide both have SPAs in the dual/triple therapy indication with metformin and/or a sulfonylurea. The PSD for dulaglutide (Para 7.1, dulaglutide PSD, July 2020 PBAC meeting) indicates that a SPA was recommended for the use of dulaglutide with insulin and metformin, although at the time of the evaluation the effective price was unknown.

Drug cost/patient/year

6.44 The estimated drug cost per patient per year for semaglutide 0.5 mg or 1.0 mg once weekly was $1,732, based on a published DPMQ per script of $132.83 with 13.04 scripts/patient/year (365.25/28 days treatment per script).

6.45 The estimated drug cost per patient per year for dulaglutide 1.5 mg once weekly was $1,732, based on published DPMQ per script $132.83 with 13.04 scripts/patient/year (365.25/28 days treatment per script). Dulaglutide costs were used in the cost-minimisation analysis.

6.46 The estimated cost per patient per year for exenatide 10 mcg twice daily is $1,101, based on published DPMQ per script $90.47, with 12.18 scripts/patient/year (365.25/30 days treatment per script). Exenatide costs were used in the financial estimates.

Estimated PBS usage & financial implications

6.47 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 for use with insulin and metformin. The estimated budget impact was based on published PBS prices, given uncertainties around the yet-to-be determined effective price for dulaglutide in combination with insulin and metformin.

6.48 At the time of evaluation, dulaglutide was not PBS-listed for use in combination with insulin and metformin. The submission presented an analysis of the expected utilisation and cost of semaglutide based on substitution of exenatide twice-daily, as it was the only GLP-1 RA PBS-listed for use in combination with insulin and metformin. The submission noted that any substitution for future use of dulaglutide would be cost neutral, given the same DPMQ (published and effective) is requested for semaglutide.

6.49 The submission estimated the market for exenatide in combination with insulin glargine, in the absence of a semaglutide listing, using a 10% Medicare sample extrapolated over the 6 years of listing. Uptake of semaglutide was assumed to come only from this market, although uptake from patients who would otherwise be treated with other diabetes medicines in combination with insulin glargine (such as gliptins, SGLT2 inhibitors or alternative insulin regimens) was considered in a sensitivity analysis.

Table 13: Key inputs for financial estimates

Data	Value	Source	Comment
Exenatide scripts in absence of semaglutide listing (in combination with insulin glargine)			
Total exenatide 5 mcg and 10 mcg twice daily scripts	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][2] Yr 4: [redacted][2] Yr 5: [redacted][3] Yr 6: [redacted][3]	10% Medicare sample analysis extrapolated using average annual absolute change in pack volumes between 2016 and 2019 over 6 years of listing (Year 1 = 2020), and multiplied by 10 to represent entire Australian population estimates.	It is likely that the negative growth for exenatide in 2018-2019 depicted in the 10% Medicare sample analysis is due to rapid uptake of dulaglutide with insulin captured in the same analysis. This rapid uptake of dulaglutide was not accounted for in the submission's projections of the GLP-1 RA with insulin market. It is unclear whether the methodology used in the 10% Medicare Sample analysis accurately captured concurrent use of exenatide (in any form) with insulin glargine, or whether some consecutive use was also captured.
Exenatide once weekly total scripts	Yr 1: [redacted][4] Yr 2: [redacted][4] Yr 3: [redacted][4] Yr 4: [redacted][5] Yr 5: [redacted][5] Yr 6: [redacted][5]	10% Medicare sample analysis (use outside of PBS restriction), extrapolated using average annual absolute change in pack volumes between 2017 and 2019, and multiplied by 10 to represent entire Australian population estimates.	
Semaglutide utilisation			
Uptake rate from exenatide twice daily	Yr 1: 10% Yr 2: 25% Yr 3: 50% Yr 4: 50% Yr 5: 50% Yr 6: 50%	Assumption, based on assumed substitution of main comparators (exenatide once weekly and dulaglutide once weekly) from semaglutide dual/triple therapy submission to PBAC, November 2019	Likely to underestimate uptake in practice but difficult to ascertain accurate estimates given shifting market dynamics.
Uptake rate from exenatide once weekly	Yrs 1-6: 10%	Assumption, based on low-level use outside of PBS restriction reported in 10% Medicare Sample Analysis	The substituted scripts are from a subgroup of exenatide once-weekly patients who are also using insulin glargine (with some use potentially outside of current PBS restrictions). It is likely that patients initiating treatment with a GLP-1 RA and insulin will choose a PBS-listed treatment regimen, and uptake from this group will be greater than 10%.

Source: Table 4.1.1, p106; Table 4.1.2, p107 of the submission, Attachment 7 (Excel spreadsheet) to the submission
Abbreviations: DPMQ, dispensed price for maximum quantity
The redacted values correspond to the following ranges:
[1] *70,000 to < 80,000*
[2] *60,000 to < 70,000*
[3] *50,000 to < 60,000*
[4] *30,000 to < 40,000*
[5] *20,000 to < 30,000*

6.50 Estimated use and financial implications are presented in the table below.

Table 14: Estimated use and financial implications

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Utilisation of exenatide (with insulin) in absence of semaglutide (scripts from 10% Medicare sample x 10)						
Exenatide 5 mcg twice daily	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Exenatide 10 mcg twice daily	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Total exenatide twice daily	[redacted][6]	[redacted][6]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]
Exenatide 2 mg once weekly	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][8]
Uptake of semaglutide (with insulin) from exenatide (scripts)						
Semaglutide uptake from exenatide twice daily	10%	25%	50%	50%	50%	50%
Semaglutide uptake from exenatide once weekly	10%	10%	10%	10%	10%	10%
Total semaglutide scripts [a]	[redacted][1]	[redacted][8]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][8]
Cost of semaglutide scripts (published)	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]
Patient copayments	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]
Total cost (published) less copayments	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]
Change in number and costs of exenatide scripts						
Exenatide 5 mcg twice daily	-[redacted][9]	-[redacted][9]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][9]
Exenatide 10 mcg twice daily	-[redacted][2]	-[redacted][1]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Exenatide 2 mg once weekly	-[redacted][9]	-[redacted][9]	-[redacted][9]	-[redacted][9]	-[redacted][9]	-[redacted][9]
Total exenatide scripts	-[redacted][1]	-[redacted][8]	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][8]
Total cost of exenatide	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Total patient copayments	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Total cost excluding copay	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]	-$[redacted][10]
Net cost to the PBS/RPBS						
Net cost (published) with copayments	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]
Net cost (published) less copayments	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]

Source: Attachment 7 of the submission

[a] Script adjustment factor of 1.1 applied to account for differences in script durations between treatments (13.0 packs per year for semaglutide vs 12.2 packs/year for exenatide).

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000
[2] 5,000 to < 10,000
[3] 60,000 to < 70,000
[4] 50,000 to < 60,000
[5] 40,000 to < 50,000
[6] 70,000 to < 80,000
[7] 30,000 to < 40,000
[8] 20,000 to < 30,000
[9] 500 to < 5,000
[10] $0 to < $10 million

6.51 The total cost to the PBS/RPBS of listing semaglutide was estimated to be up to $0 to < $10 million in Year 3, declining to $0 to < $10 million in Year 6, and a total of $0 to < $10 million over the first 6 years of listing. The submission stated that the positive net cost of listing is based on the proposed published price of semaglutide, but with the

proposed effective price the same as the (as yet unknown) effective price for dulaglutide in this indication, the net cost to government will be zero.

6.52 The evaluation considered that the estimates of utilisation are likely to be underestimated for the following reasons:

- It is likely that the negative growth for exenatide in 2018-2019 depicted in the 10% Medicare sample analysis is due to rapid uptake of dulaglutide with insulin (± metformin) captured in the same analysis. Using the dispensed volumes of dulaglutide in conjunction with insulin reported in the analysis (multiplied by ten to extrapolate to the entire population), there were 10,000 to < 20,000 dulaglutide scripts dispensed in 2018, increasing considerably to 70,000 to < 80,000 scripts dispensed in 2019 (Table 4.1, Attachment 8 of the submission). In the same time period, the scripts for exenatide twice daily decreased from 80,000 to < 90,000 to 80,000 to < 90,000; and for exenatide once weekly decreased from 50,000 to < 60,000 to 30,000 to < 40,000 scripts. The PBAC noted this rapid uptake of dulaglutide was not accounted for in the submission's projections of the GLP-1 RA with insulin market. The addition of newer agents is likely to contribute to overall market growth.
- The proposed restriction allows use of semaglutide with insulin formulations other than insulin glargine, which were not included in the estimation of insulin-treated T2DM patients in the 10% Medicare sample analysis. The submission's estimates included 200,000 to < 300,000 patients with T2DM treated with insulin glargine at least once between 2011 and 2019. However, there were 200,000 to < 300,000 patients with T2DM registered with the National Diabetes Services Scheme (NDSS) as insulin users in 2020 (Diabetes data snapshots, September 2020[3]). This indicates the potential for greater patient numbers due to higher than predicted number of eligible patients with T2DM where insulin treatment is necessary.
- Uptake rates of semaglutide from the exenatide twice daily market were assumptions, and likely underestimates of uptake in practice, given the once weekly versus twice daily dosing schedule. However, it is difficult to ascertain accurate estimates of uptake given shifting market dynamics in the GLP-1 RA market.
- Uptake rates of semaglutide from the exenatide once weekly market were low, with the submission arguing that there would be no advantage to swap from one once-weekly formulation to another. However, it is likely that doctors initiating treatment with a GLP-1 RA in combination with insulin will choose a PBS-listed once-weekly treatment.
- The submission assumed that compliance will not be substantially different between semaglutide and the substituted therapy, but it is likely that there will be

[3] https://www.ndss.com.au/about-the-ndss/diabetes-facts-and-figures/diabetes-data-snapshots/

greater compliance with once weekly injections for semaglutide over twice-daily injections for exenatide.

6.53 The submission included a number of sensitivity analyses, including:

- Substitution rates with semaglutide (doubled base case rates, including 100% substitution of exenatide twice daily from year 3 onwards)
- Growth rates for current GLP-1 RA market (based on exenatide twice daily/once weekly growth from 2018-19; or previous 5 years from 2014-2019)
- Substitution of a range of other (non-GLP-1 RA) diabetic medicines used in combination with basal insulin (1% in year 1 rising to 6% in year 6).

6.54 The submission's estimates were most sensitive to the substitution of other non-GLP-1 RA diabetes medicines, with 6% uptake from these medicines in Year 6 of listing resulting in a net cost to Government of $20 million to < $30 million, compared to $0 to < $10 million in the base case (based on the published DPMQ for semaglutide).

Quality Use of Medicines

6.55 The sponsor did not provide any information on quality use of medicines factors. The product information for semaglutide and additional post-market surveillance safety data include special warnings and precautions with semaglutide due to its safety profile, particularly surrounding the management of gastrointestinal adverse events and diabetic retinopathy.

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

7 PBAC Outcome

7.1 The PBAC recommended extending the existing listing of semaglutide to include the treatment of Type 2 Diabetes Mellitus (T2DM) in combination with insulin and metformin unless contraindicated or not tolerated. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of semaglutide (both 0.5 mg once weekly and 1.0 mg once weekly) under the requested restriction would be acceptable if it was cost-minimised against dulaglutide 1.5 mg once weekly.

7.2 The PBAC accepted that dulaglutide once weekly was the appropriate main comparator, and exenatide twice daily was the appropriate secondary comparator.

7.3 The PBAC noted that the submission presented data from three key placebo-controlled trials, SUSTAIN 5 (semaglutide versus placebo with concomitant basal insulin), AWARD-9 (dulaglutide versus placebo with concomitant insulin glargine) and GWCO (exenatide versus placebo with concomitant insulin glargine). The PBAC considered that the active-controlled lixisenatide with insulin glargine trial (LIXILAN-L) was not relevant for this submission. The PBAC noted that the submission was based on indirect comparisons of SUSTAIN 5 (n=397) with AWARD-9 (n=300) and GWCO (n=261), with placebo as the common reference arm. Across all trials, between 81%

and 90% of patients in each treatment arm were also receiving concomitant metformin.

7.4 Based on the indirect comparisons for the primary outcome, the PBAC noted that both semaglutide treatment arms had a statistically significantly greater reduction from baseline in HbA1c compared to dulaglutide and exenatide. The PBAC noted that the submission nominated a non-inferiority margin of 0.3% to 0.4% and that the point estimates for the mean differences with both semaglutide doses exceeded this threshold (see Table 7).

7.5 The PBAC also noted that the submission highlighted that these point estimates exceeded 0.5%, previously considered by the PBAC to be a potentially relevant minimal clinically important difference (MCID) for testing superiority (paragraph 7.5, semaglutide PSD, November 2019). The PBAC had concerns with this statement given that the HbA1c changes (versus placebo) across the three trials were variable, i.e. there was no change in HbA1c for placebo in SUSTAIN 5, whilst there was a reduction from baseline in the other trials (see Tables 7 and 9). The PBAC considered that this variation in placebo group outcomes could be attributed to the more restrictive insulin titration algorithm in SUSTAIN 5, which may limit the exchangeability of the trials for the indirect analysis. The pre-PBAC response argued that, for the purpose of the submission, a conservative claim of non-inferiority (rather than superiority) was made with respect to relative effectiveness. Overall, the PBAC accepted that semaglutide once weekly demonstrated non-inferior clinical effectiveness compared to dulaglutide once weekly and exenatide twice daily.

7.6 The PBAC noted there were no significant differences in the indirect comparison of safety outcomes with the exception of a higher rate of documented hypoglycaemia events in patients treated with semaglutide 0.5 mg or 1.0 mg compared with dulaglutide, but considered this could also be attributed to the more restrictive insulin titration algorithms in SUSTAIN 5. Overall, the PBAC was satisfied that semaglutide once weekly demonstrated non-inferior safety to dulaglutide once weekly and exenatide twice daily.

7.7 The recommended equi-effective doses for the cost-minimisation to dulaglutide are as follows: when used in combination with metformin (unless contraindicated or not tolerated) and insulin, semaglutide (0.5 mg once weekly and 1.0 mg once weekly) is equi-effective to dulaglutide 1.5 mg once weekly.

7.8 The PBAC noted that the pre-PBAC response claimed that, due to the request that semaglutide once weekly be cost-minimised to dulaglutide once weekly, it is anticipated that semaglutide will substitute for dulaglutide and will not grow the GLP-1 RA market. The PBAC considered it was likely true that the listing of semaglutide in combination with insulin should be cost neutral. However, the PBAC considered that the overall GLP-1 with insulin market may have been underestimated given the recent listing of dulaglutide in combination with insulin was not accounted for in the utilisation estimates.

7.9 The PBAC advised that the cost per patient per year of semaglutide should be the same as dulaglutide.

7.10 The PBAC recommended that the restrictions for semaglutide be consistent with the current listings of dulaglutide once weekly and exenatide (5 mcg and 10 mcg) twice daily for the same indication.

7.11 The PBAC noted that the Early Supply Rule applies to dulaglutide and exenatide, and recommended that it should also apply to semaglutide.

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

7.13 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 restriction to semaglutide (12080T and 12075M) as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty Packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
SEMAGLUTIDE semaglutide 1.34 mg/mL injection, 1 x 1.5 mL pen device	12080T	1	1	5	Ozempic®	Novo Nordisk
semaglutide 1.34 mg/mL injection, 1 x 3 mL pen device	12075M	1	1	5	Ozempic®	Novo Nordisk

Restriction Summary 5469 / Treatment of Concept: 5469	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners
	Restriction type: ☒Authority Required – Streamlined [5469]
	Indication: Diabetes mellitus type 2
	Clinical criteria:
	The treatment must be in combination with insulin
	AND
	Clinical criteria:
	The treatment must be in combination with metformin unless contraindicated or not tolerated
	AND
	Clinical criteria:
	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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
	Prescribing 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.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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), or an SGLT2 inhibitor.
	Administrative Advice: Special Pricing Arrangements apply.

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.