

## 5.16 SEMAGLUTIDE,

**Injection 0.25 mg, 0.5 mg and 1.0 mg in 0.5 mL pre-filled single dose pen**

**Injection 1.7 mg and 2.4 mg in 0.75 mL pre-filled single dose pen,**

**Wegovy<sup>®</sup>,**

**Novo Nordisk Pharmaceuticals Pty. Limited**

### 1 Purpose of submission

1.1 The Category 2 submission requested a Section 85 (General Schedule) PBS listing for semaglutide 2.4 mg for the treatment of severe obesity. The PBAC has not previously considered semaglutide for this indication. Semaglutide 1.0 mg is currently listed on the PBS for the treatment of type 2 diabetes. (Note: 2.4 mg and 1.0 mg refer to the respective maintenance doses, the actual strengths requested in this submission are shown in the 'Requested listing' section).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo.

**Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)**

Component	Description
Population	Adult patients with BMI $\geq$ 35 kg/m <sup>2</sup> and at least one weight-related comorbidity but who do not have diabetes.
Intervention	Semaglutide subcutaneous injection once weekly. The recommended starting dose is 0.25 mg, with stepped dose escalation to 0.5 mg after 4 weeks, 1 mg after another 4 weeks, 1.7 mg after another 4 weeks, and then to 2.4 mg as the maintenance dose. To be used in conjunction with diet and exercise.
Comparator	Placebo. To be used in conjunction with diet and exercise.
Outcomes	Reduction in weight, improvement in cardiometabolic risk factors, reduced incidence of downstream complications (diabetes, cardiovascular disease, knee osteoarthritis, obstructive sleep apnoea), increased survival, improved quality of life and reduced healthcare resource utilisation.
Clinical claim	Semaglutide 2.4 mg is superior in terms of efficacy and inferior in terms of safety compared to placebo.

Source: Table 1-1 (p 16) of the submission

## 2 Background

### **Registration status**

2.1 Semaglutide 1.0 mg is TGA registered for the “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 or in addition to other medicinal products for the treatment of type 2 diabetes”.

- 2.2 Semaglutide 2.4 mg was submitted under the TGA/PBAC parallel process with a proposed indication “as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of:
- $\geq 30 \text{ kg/m}^2$  (obesity); or
  - $\geq 27 \text{ kg/m}^2$  to  $<30 \text{ kg/m}^2$  (overweight) in the presence of at least one weight-related comorbidity”.
- 2.3 **TGA status at time of PBAC consideration:** The second round TGA clinical evaluation report, delegate’s overview and draft product information for semaglutide were available during the evaluation and ESC consideration. The ACM meeting outcomes were available at the time of PBAC consideration.
- 2.4 The TGA delegate considered that semaglutide has a favourable benefit-risk profile for the proposed indication but noted the lack of long-term data beyond two years and the potential for rebound following treatment discontinuation (although the delegate noted that the current data suggests a return to baseline rather than rebound).
- 2.5 The ACM supported registration and considered there was a positive benefit-risk profile for the following indication (amendments underlined):
- “WEGOVY, when used as an adjunct to a reduced-energy diet and increased physical exercise, is indicated for induction and maintenance of weight loss in adults with an initial Body Mass Index (BMI) of:
- $\geq 30 \text{ kg/m}^2$  (obesity); or
  - $\geq 27 \text{ kg/m}^2$  to  $< 30 \text{ kg/m}^2$  (overweight) in the presence of at least one weight related comorbidity.”
- 2.6 The ACM was also supportive of a Category D pregnancy classification with further emphasis in the Product Information on importance of contraception / not attempting conception or pregnancy while on treatment, particularly as weight-loss may be used as an aid for fertility.
- 2.7 Semaglutide 2.4 mg was approved by the US Food and Drug Administration in June 2021 and received a positive recommendation from the European Medicines Agency in November 2021 for similar indications.

### ***PBS stakeholder meeting***

- 2.8 A stakeholder meeting was held on 26 August 2021 to discuss the use of pharmacotherapy (particularly semaglutide) for weight management in overweight/obese patients on the PBS. Attendees included PBAC members, clinicians and consumer groups as well as representatives from the Obesity Collective, Novo Nordisk and the Department of Health. The discussion covered a variety of topics including burden of disease, treatment accessibility, the population suitable for PBS

access to pharmacotherapy (including clinical criteria for initiation and continuation, authority levels and prescriber types), use of prior therapies and goals of treatment.

- 2.9 A summary of the outcomes of the stakeholder meeting is available at: <https://www.pbs.gov.au/info/news/2021/11/semaglutide-wegovy-stakeholder-meeting-outcome-statement>

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

### **3 Requested listing**

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. Note, the Secretariat revisions below do not include PBAC advice on defining the eligible population.

Public Summary Document – March 2022 PBAC Meeting

Initial – dose titration

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEMAGLUTIDE					
0.25 mg/0.5 mL injection, 4 x 0.5 mL pen devices	NEW	4	1	0	Wegovy
0.5 mg/0.5 mL injection, 4 x 0.5 mL pen devices		4	1	0	
1 mg/0.5 mL injection, 4 x 0.5 mL pen devices		4	1	0	
1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices		4	1	0	
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code] <input type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Indication:</b> Obesity					
<b>Treatment Phase:</b> Initial treatment – dose titration					
<b>Clinical criteria:</b>					
Patient must have a Body Mass Index greater than or equal to 35 kg/m <sup>2</sup>					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have a <i>confirmed</i> diagnosis of at least one of the following weight related comorbidities recorded in their medical records: dyslipidaemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnoea, impaired glucose tolerance, impaired fasting glucose, elevated HbA1c, menstrual disorder, polycystic ovarian syndrome, involuntary impaired fertility, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, kidney disease, symptomatic osteoarthritis of the hip or knee, hyperuricaemia or gout, thyroid disease, asthma or chronic obstructive pulmonary disease					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not have type II diabetes mellitus					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must not receive more than 28 weeks of treatment under this restriction. The treatment must not exceed 16 weeks of dose titration under this restriction					
<b>Treatment criteria:</b>					
Patient must be receiving, or enrolled to receive, dietetic and weight management advice. The treatment must be adjunct to receiving dietetic and weight management advice as part of a multidisciplinary care team.					
<b>Population criteria:</b>					
Patient must be aged 18 years or older					
<b>Prescribing Instructions:</b> An initial baseline value of body weight and Body Mass Index must be recorded in the patient's medical record. A confirmed diagnosis of at least one of the above-mentioned weight-related comorbidities must be recorded in the patient's medical record.					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

Public Summary Document – March 2022 PBAC Meeting

	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

Initial – dose maintenance

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEMAGLUTIDE					
1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices	NEW	1	4	3	Wegovy
2.4 mg/0.75 mL injection, 4 x 0.75 mL pen devices		1	4	3	
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code] <input type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
<b>Indication:</b> Obesity					
<b>Treatment Phase:</b> Initial treatment – dose maintenance					
<b>Clinical criteria:</b> Patient must have completed the initial PBS-subsidised 16-week dose titration with this drug for this condition					
<b>AND</b>					
<b>Clinical criteria:</b> The treatment must not exceed 16 weeks of dose maintenance under this restriction					
<b>Treatment criteria:</b> The treatment must be adjunct to receiving dietetic and weight management advice as part of a multidisciplinary care team					
<b>Population criteria:</b> Patient must be aged 18 years or older					
<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					

Continuing – First continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEMAGLUTIDE					
1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices	NEW	1	4	5	Wegovy
2.4 mg/0.75 mL injection, 4 x 0.75 mL pen devices		1	4	5	
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners					

Public Summary Document – March 2022 PBAC Meeting

	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code] <input type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	<b>Indication:</b> Obesity
	<b>Treatment Phase:</b> First continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received initial PBS subsidised treatment with this drug for this disease Patient must have completed the initial – dose maintenance PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have reduced their initial body weight by 5% during treatment with this drug Patient must have maintained a reduction of at least 5% from the initial baseline body weight while being treated with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 24 weeks of treatment under this restriction The treatment must not exceed 24 weeks under this restriction
	<b>Treatment criteria:</b>
	Patient must be receiving, or enrolled to receive, dietetic and weight management advice The treatment must be adjunct to receiving dietetic and weight management advice as part of a multidisciplinary care team
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<b>Administrative Advice:</b> For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

Continuing – Subsequent continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEMAGLUTIDE					
1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices	NEW (same as first continuing)	1	4	5	Wegovy
2.4 mg/0.75 mL injection, 4 x 0.75 mL pen devices		1	4	5	

Restriction Summary [new] / Treatment of Concept: [new]

	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code] <input type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	<b>Indication:</b> Obesity

Public Summary Document – March 2022 PBAC Meeting

	<b>Treatment Phase:</b> Subsequent continuing treatment
	<b>Clinical criteria:</b>
	<p>Patient must have previously received the first continuing PBS-subsidised treatment with this drug for this disease</p> <p>Patient must have completed the first continuing PBS-subsidised treatment with this drug for this condition at their most recent treatment course</p> <p>OR</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition under this restriction</p>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<p>Patient must have reduced their initial body weight by 10% during treatment with this drug</p> <p>Patient must have maintained a reduction of at least 10% from the initial baseline body weight while being treated with this drug for this condition</p>
	<b>AND</b>
	<b>Treatment criteria:</b>
	<p><del>Patient must be receiving, or enrolled to receive, dietetic and weight management advice</del></p> <p>The treatment must be adjunct to receiving dietetic and weight management advice as part of a multidisciplinary care team</p>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
	<b>Administrative Advice:</b> For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

- 3.2 The submission requested a Special Pricing Arrangement for semaglutide consisting of an 1% rebate on the published DPMQ (\$1) per script. The proposed effective DPMQ of semaglutide 2.4 mg for obesity (\$1) was substantially higher than the current effective DPMQ of semaglutide 1.0 mg for type 2 diabetes (\$1).
- 3.3 The proposed PBS restriction ( $\geq 35$  BMI with at least one comorbidity) was narrower than the proposed TGA indication, treatment guidelines and the key clinical trials ( $\geq 30$  BMI OR  $\geq 27$  BMI with at least one comorbidity). The proposed restriction was also narrower than the submission's clinical management algorithm ( $\geq 35$  BMI OR  $\geq 30$  BMI with at least one serious comorbidity).
- 3.4 The submission claimed that the target subgroup population was chosen as a pragmatic compromise encompassing multiple considerations of clinical need, potential to benefit, cost effectiveness and financial impact. The submission did not document these considerations, but the pre-PBAC response reiterated this claim. Insufficient data were provided in the submission to adequately compare the clinical need (quality of life and risk of downstream complications without treatment),

potential to benefit (quality of life and risk of downstream complications with treatment), cost-effectiveness, or affordability between the target subgroup and other potential subgroups based on different BMI and comorbidity thresholds. The Pre-Sub-Committee Response (PSCR) stated that the criteria were influenced by the stakeholder meeting, where it was noted that participants in the STEP trials had a mean BMI  $\geq 35$  kg/m<sup>2</sup> and that weight loss was similar across BMI subgroups.

- 3.5 No justification was provided in the submission for the chosen list of comorbidities. The PSCR stated that the list of comorbidities proposed in the restriction was chosen to match those deemed to be “weight related” by the investigators in the STEP trials. In the trials, the presence of specific comorbidities (diabetes, hypertension, dyslipidaemia, obstructive sleep apnoea and cardiovascular disease) was an eligibility criterion for patients with a BMI  $\geq 27$  kg/m<sup>2</sup> but  $< 30$  kg/m<sup>2</sup>; while those with BMI  $\geq 30$  kg/m<sup>2</sup> were enrolled in the trial irrespective of number or nature of comorbidities. Based on individual patient data from the STEP-1 trial, 79% of patients with a baseline BMI  $\geq 35$  kg/m<sup>2</sup> had a screened comorbidity at baseline, with a further 17% having high cardiovascular risk factors that would be likely to qualify them for treatment in clinical practice (total cholesterol  $> 5$  mmol/L OR HDL  $< 1.0$  mmol/L in males or  $< 1.3$  mmol/L in females OR systolic blood pressure  $> 140$  mmHg). As a consequence, the ESC advised that the application of a broad comorbidity definition in combination with a sufficiently high baseline BMI threshold appears to provide little added value in defining the target population. The pre-PBAC response claimed that semaglutide has similar outcomes across BMI/risk factor subgroups (except for type 2 diabetes) and thus provide little guidance for narrowing the target population. The PBAC advised that a much more targeted approach would likely be necessary to assure cost-effectiveness based on the STEP trials, in association with a multidisciplinary approach to obesity (see paragraph 3.11).
- 3.6 The proposed restriction specifically excludes patients with type 2 diabetes. The submission claimed that this was reasonable as these patients already have access to therapies with weight loss effects (e.g. GLP-1 analogues). The submission also noted that the weight reduction observed in diabetic patients was typically smaller than that observed for non-diabetic patients in the key clinical trials. The PSCR claimed that their exclusion would thus “provide a more cost-effective and affordable listing scenario”. The ESC considered that exclusion of diabetic patients on the basis that lower doses of GLP-1 analogues are already available on the PBS (for some patients) and that the weight reduction was lower in the diabetic population was an inadequate justification. The ESC noted that this raised questions of inequitable access.
- 3.7 The submissions observations with respect to type 2 diabetes were based on informal comparisons between trials and do not account for other differences between populations (such as gender ratio) which may affect the reported results. Additionally, the submission did not address the value of weight loss in each of the populations and it is unclear whether weight loss in diabetic patients has a smaller, similar or greater impact on downstream complications compared to non-diabetic patients. Overall, the

ESC advised that the exclusion of patients with type 2 diabetes was not justified as these patients achieved a response in the key clinical trial, and their exclusion raises an important equity of access issue given that the proposed restriction would allow the vast majority of other patients with severe obesity (including patients with pre-diabetes) subsidised access to the more effective 2.4 mg semaglutide dose, while patients with diabetes who meet the existing PBS eligibility criteria would be restricted to the less effective 1.0 mg semaglutide dose and other similar GLP-1 analogues.

- 3.8 The submission proposed two continuation rules: restricting treatment to patients who achieve a 5% weight reduction by 28 weeks (including a 16-week titration period) and restricting treatment to patients who achieve a 10% weight reduction by 52 weeks. The submission claimed that these rules allow subsidised treatment to be targeted to the population who are receiving a clinically meaningful benefit. A reduction in body weight of at least 5% over an observation period of at least 1 year is widely accepted as a clinically important change and was used as a primary outcome in the clinical trials. The submission did not address the relevance and usefulness of continuation criteria given that patients may, under the proposed listing, initiate multiple cycles of semaglutide and therefore continue to receive therapy without meeting the continuation rules. The ESC considered that it was highly likely that patients would access semaglutide intermittently and repeatedly, given the rapid weight gain that occurs after cessation of the drug, and that this would very likely impact negatively on the potential for downstream benefits and hence the cost effectiveness of semaglutide.
- 3.9 The submission requested an Authority Required (Streamlined) restriction level, based on the size of the target population and the simple restriction criteria. The ESC considered that a Streamlined Authority listing would result in a high risk of use outside the requested restriction (given that the clinical trial evidence and treatment guidelines suggest use in broader populations) as well as the risk of ongoing use in patients not achieving nominated weight reduction thresholds. The ESC noted that this would reduce overall cost-effectiveness.
- 3.10 There were a number of additional issues with the restriction (inconsistency in the repeats between initiation/continuation scripts, lack of dose flexibility and inconsistency with MBS listing for bariatric surgery). The text of the submission also indicated that the sponsor was proposing nurse practitioner prescribing for treatment continuation, however, this was omitted from the restriction.
- 3.11 The ESC considered that the requirements in relation to diet and exercise advice were unclear. The proposed restriction (on all phases) included a treatment criterion requiring patients be receiving, or enrolled to receive, dietic and weight management advice. It was unclear why a patient only enrolled to receive diet/weight advice, and not actually receiving the advice, would be an appropriate candidate for treatment. The restriction did not require patients to have any previous “unsuccessful” attempts at weight loss using diet and exercise, although the ESC recognised this may be difficult

to define. The ESC agreed with the evaluation that it would be appropriate to require patients to be managed by a multidisciplinary care team. Overall, although the ESC recognised potential equity issues with accessing multidisciplinary care, it considered that the broad criteria proposed for the PBS listing did not reflect the intensity of diet and exercise counselling seen in the key clinical trials. Furthermore, the ESC advised that pharmacotherapy for obesity should not be subsidised as a unidimensional solution, and a whole of health system approach was required. The PBAC agreed with ESC, and noting the *National Obesity Strategy 2022-2032* encompasses a range of interventions, not just pharmacotherapy, any resubmission for semaglutide would be need to considered in this context.

## 4 Population and disease

- 4.1 Obesity is a “chronic relapsing disease process” (World Obesity Federation, 2017). It is characterised by excessive fat accumulation which is typically caused by a sustained imbalance between energy intake (from the diet) and energy expenditure (through physical activities and bodily functions). There are many different genetic, lifestyle and social factors that may influence the energy balance of individuals such as metabolic efficiency, medical conditions/medications, active or sedentary habits, diet (quantity and frequency of consumption of food and flavoured drinks), the availability of convenience foods, the built environment etc.
- 4.2 Obesity is typically diagnosed based on body mass index (BMI; ratio of weight to height<sup>2</sup>) and/or waist circumference. A BMI between 30 and 34.9 kg/m<sup>2</sup> is considered obese and a BMI of 35 kg/m<sup>2</sup> and above is considered severely obese. Clinical guidelines also note the need to adjust BMI thresholds for different patient populations, with lower thresholds recommended for individuals of Asian or Aboriginal ancestry (Australian Obesity Management Algorithm 2016). In Caucasian men a waist circumference of 94/102 centimetres or more has been shown to indicate an increased/greatly increased risk of weight-related comorbidities. In Caucasian women a waist circumference of 80/88 centimetres or more has been shown to indicate an increased/greatly increased risk of weight-related comorbidities (WHO, 2011).
- 4.3 Obesity is highly prevalent in the Australian population and has been steadily increasing over time with the latest estimate indicating that approximately 1 in 3 adults are living with obesity (ABS National Health Survey 2017-2018).
- 4.4 Patients with obesity may experience a reduction in quality of life due to physical limitations on daily activities as well as other psychosocial impacts (such as stigmatisation and discrimination associated with obesity). Obesity is also a major risk factor associated with the development of a number of other conditions including diabetes, cardiovascular disease, osteoarthritis, gastro-oesophageal reflux disease, obstructive sleep apnoea, non-alcoholic steatohepatitis, urinary incontinence, polycystic ovary syndrome and some cancers.

- 4.5 In clinical practice, the first-line management of obesity typically involves weight management advice to improve diet and increase physical activity as well as addressing any other conditions that may affect or be affected by obesity. Additional lifestyle interventions such as low energy diets (using meal replacements) and intensive behavioural therapy are also sometimes used in practice. Pharmaceutical and surgical treatments are typically considered as later-line therapies in patients requiring further weight loss support. The stakeholder meeting noted that in hospital and other specialist settings, patients can also require short term weight loss in order to be eligible for transplant or other surgery. However, despite the available treatment options, many patients with obesity do not maintain weight loss over time and instead cycle between weight loss and weight gain.
- 4.6 Semaglutide is a long-acting glucagon-like peptide 1 receptor agonist (GLP-1 analogue). Semaglutide reduces blood glucose by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner. The exact mechanism by which semaglutide reduces body weight is unclear but is thought to be related to lower energy intake due to an overall reduction in appetite. The ESC noted it is unclear what role ongoing gastrointestinal adverse events play in maintaining the loss of weight.
- 4.7 Treatment with semaglutide 2.4 mg is intended to be used as an adjunct to lifestyle modification, incorporating elements of a reduced calorie diet and increased physical activity. The submission intended that semaglutide would ideally be used as a chronic therapy in order to maintain weight improvements over time. However, given the cyclical nature of weight loss and weight gain, and the adverse event profile, patients may receive multiple cycles of semaglutide therapy rather than remain on therapy over a longer continuous treatment duration.
- 4.8 The submission claimed that there is a clinical need for semaglutide 2.4 mg given that few people living with obesity manage to achieve and maintain weight loss through lifestyle modification alone. The submission claimed that current treatment options are insufficient given the modest weight loss associated with existing pharmacotherapies (which are not PBS listed) and the limited access to more effective surgical options through the hospital systems.
- 4.9 The PBAC noted that the *National Obesity Strategy 2022-2032* was released on 4 March 2022, the week prior the PBAC meeting. It is a 10-year framework for action to prevent, reduce, and treat, overweight and obesity in Australia. It focuses on prevention, but also includes actions to better support Australians who are living with overweight or obesity, to live their healthiest lives.

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

## 5 Comparator

- 5.1 The submission nominated placebo (as a proxy for no pharmacological therapy) in conjunction with diet and exercise as the main comparator. The main argument provided in support of this nomination was that while semaglutide is positioned in the same place in therapy as existing pharmacotherapies (liraglutide, naltrexone/bupropion, phentermine and orlistat), these treatments have not been assessed by the PBAC for the treatment of obesity and they are likely to be less effective and less cost-effective than semaglutide 2.4 mg. This claim was not adequately supported (no clinical or economic comparisons against other pharmacotherapies were presented in the submission). Nevertheless, it is likely that these therapies are not widely used in clinical practice and therefore it may be reasonable to consider placebo in conjunction with diet and exercise as the main comparator.
- 5.2 The DUSC noted that in a recent meta-analysis published in *The Lancet* on 8 December 2021, "Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials", phentermine–topiramate was the most effective in lowering weight, followed by GLP-1 receptor agonists. Of these, "semaglutide might be the most effective".
- 5.3 The ESC advised that the role of a multidisciplinary care team in the management of obesity was not sufficiently defined in the comparator or intervention aspects of the submission. The ESC noted that the economic evaluation included costs of weight management advice based on MBS costs and the assumption that all patients in both arms would receive monthly dietician visits over the 20-year model duration. The submission estimated annual weight management costs for both treatment arms based on the assumption that patients would visit a dietician 12 times each year. The cost of a dietician visit was estimated based on MBS item 10954 (dietician visit under a Team Care Arrangement). The assumption of 12 dietician visits per year was consistent with the clinical trial data but is highly unlikely to reflect Australian clinical practice. As an example, the MBS item nominated by the submission is limited to a maximum of 5 visits per year which is shared between dieticians and other allied health providers. The availability of dieticians, especially in rural/regional communities, is often very limited and would be highly unlikely to be able to meet this expectation. The pre-PBAC response proposed that 11 counselling sessions could be conducted per year comprising of 6 general practice consultations over 7 months of dose titration/maintenance, followed by 5 MBS-funded dietician services.
- 5.4 The PBAC noted that the submission had positioned bariatric surgery as a second-line treatment option in patients with BMI  $\geq 45$  kg/m<sup>2</sup> or as a third-line option after pharmacotherapy in less severe patients. The PBAC noted the advice of the stakeholder forum that bariatric surgery is primarily delivered in private hospitals, with less than 10% being delivered in public hospitals due to long waiting times for public services, limited staff and resources and lack of/insufficient provision of public

services in regional and remote areas, where there is high need. The PBAC noted that approximately 50,000 patients received MBS-listed bariatric services annually between 2013 and 2017, that there were notable variations in the fees charged, and that out-of-pocket costs of private patients were substantial (Public Summary Document for 1180r – Review of MBS items for the surgical treatment of obesity, 2018).

*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 individuals (27), health care professionals (7) and organisations (5) via the Consumer Comments facility on the PBS website. Consumers emphasised the high burden of obesity on individuals and the health care system in Australia. Health care professionals highlighted that obesity is a difficult condition to treat with diet and exercise having only limited efficacy. The benefits of semaglutide were expected to include weight loss and a reduction in weight-related comorbidities, both physical and psychological. Some professionals expected that semaglutide would have most utility in morbidly obese patients for whom diet and exercise were ineffective. The health care professionals also highlighted the socio-economic determinants of obesity and noted that those patients most in need of treatment are also likely to be least able to afford non-PBS therapy.
- 6.3 Many individuals who provided input had experience of using off label, non-PBS subsidised semaglutide (Ozempic®) for obesity (this PBAC submission was for Wegovy®, which is not yet registered for use in Australia). Some patients had also used phentermine and liraglutide for weight loss. Individuals emphasised the impact of obesity on their lives, including negative effects on sleep, movement, joint pain, continence, and their psychological and social wellbeing. Many noted that they had underlying health conditions which contributed to weight loss or made weight loss challenging. Some expected to use semaglutide instead of bariatric surgery, or after previous surgery. Individuals using off-label Ozempic® had reported weight loss (approximately 1-2 kilograms per week), constipation and nausea, as well as one patient noting a reduction in medicines needed to manage high blood pressure. Many patients expected that losing weight would have a flow-on benefit for other health conditions. Finally, the cost of non-PBS subsidised Ozempic® was noted to be major barrier to access.
- 6.4 The PBAC also noted comments received from the Australian and New Zealand Obesity Society (ANZOS), Diabetes Australia, the Obesity Collective, the Royal Australian College of General Practitioners (RACGP) and the Weight Issues Network.

Organisations highlighted the patient and healthcare system costs of obesity. ANZOS and RACGP were strongly supportive of the availability of evidence-based pharmacotherapy for obesity treatment via the PBS, emphasising the chronic nature of the condition and current inequitable treatment access across Australia. Several organisations commented that treatment access is hindered by weight stigma and discrimination, and mirrored the comments made by health care professionals that the patients most in need of treatment are least likely to be able to access services (for financial and/or geographic reasons). It was noted by one organisation that there are no current national treatment guidelines for obesity in Australia. Several organisations also highlighted the need for obesity treatment to move beyond notions of ‘individual responsibility’, and emphasised that effective treatment required a holistic person-centred approach. Diabetes Australia was strongly supportive of the PBS listing of semaglutide for use in patients at high risk of developing type 2 diabetes and considered that the weight loss seen in the trials would be sufficient to reduce this risk in many people. The RACGP considered that semaglutide should be available via general practice, to help address current barriers to treatment access.

### Clinical trials

6.5 The submission was based on five head-to-head randomised trials comparing semaglutide to placebo in the STEP clinical trial program (STEP 1-5). The submission also provided additional supportive data from an off-treatment extension of the STEP-1 trial.

6.6 Details of the included studies are provided in Table 2 below.

**Table 2: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
NCT03548935 (STEP-1)	Novo Nordisk (2020). Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity	Internal study report
	Novo Nordisk (2021). Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity (extension phase)	Internal study report
	Novo Nordisk (2021). STEP-1 Subgroup Analysis	Internal study report
	Wilding et al (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity	<i>New England Journal of Medicine</i> 384: 989-1002
	Kushner et al (2021). Once-weekly Subcutaneous Semaglutide 2.4 mg Reduces Body Weight in Adults with Overweight or Obesity Regardless of Baseline Characteristics (STEP 1) <sup>a</sup>	<i>Journal of the Endocrine Society</i> A24 [Abstract only]. Poster provided with PSCR
NCT03552757 (STEP-2)	Novo Nordisk (2020). Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes	Internal study report
	Davies et al (2021). Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial	<i>Lancet</i> 397: 971-984
NCT03611582 (STEP-3)	Novo Nordisk (2020). Effect and safety of semaglutide 2.4 mg once-weekly as adjunct to intensive behavioural therapy in subjects with overweight or obesity	Internal study report
	Wadden et al (2021). Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial	<i>Journal of the American Medical Association</i> 325: 1403-1413

Trial ID	Protocol title/ Publication title	Publication citation
NCT03548987 (STEP-4)	Novo Nordisk (2020). Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during run-in period	Internal study report
	Rubino et al (2021). Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial	<i>Journal of the American Medical Association</i> 325: 1414-1425
NCT03693430 (STEP-5)	Novo Nordisk (2021). Two-year effect and safety of semaglutide 2.4 mg once weekly in subjects with overweight or obesity	Internal study report

Source: Table 2-3 (p 48), Figure 2-2 (p 50) of the submission

Abbreviation: PSCR, Pre-Sub-Committee Response

<sup>a</sup> Identified during evaluation

6.7 The submission noted an ongoing cardiovascular outcomes trial of semaglutide compared to placebo in patients with overweight/obesity and established cardiovascular disease (SELECT; n=17,500; estimated completion September 2023). This study was excluded from the submission as no results were available.

6.8 The results from STEP-6 (NCT03811574; semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population) were published on 4 February 2022 (Kadowaki et al., 2022, in press version). This was not reviewed by the ESC.

6.9 The key features of the included studies are summarised in Table 3 below.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
STEP-1	1,961	MC, R, DB, PC, 75 weeks duration with off-treatment extension to 120 weeks	Low	Patients who were overweight/obese without diabetes	Weight, biomarkers, quality of life and adverse events	Individual patient data from subgroup
STEP-2	1,210	MC, R, DB, AC/PC, (semaglutide 1.0 mg active control) 75 weeks duration	Low	Patients who were overweight/obese with diabetes	Weight, biomarkers, quality of life and adverse events	Not used
STEP-3	611	MC, R, DB, PC, 75 weeks duration	Low	Patients who were overweight/obese without diabetes receiving intensive behavioural therapy	Weight, biomarkers, quality of life and adverse events	Not used
STEP-4	803	MC, R, DB, PC, (treatment withdrawal study design) 75 weeks duration	Low	Patients who were overweight/obese without diabetes	Weight, biomarkers, quality of life and adverse events	Not used
STEP-5	304	MC, R, DB, PC, 104 weeks duration	Low	Patients who were overweight/obese without diabetes	Weight, biomarkers and adverse events	Not used

Source: Section 2.3.1 (p 50-52), Section 2.4 (p 60-80) of the submission

Abbreviations: AC, active-controlled; DB, double-blind; MC, multicentre; PC, placebo-controlled; R, randomised

6.10 The patient characteristics of the populations included in STEP-1, STEP-3 and STEP-5 trials were broadly similar, with a mean age of 46 or 47 years, and mostly being white,

female, with obesity (BMI > 30 kg/m<sup>2</sup>) and with multiple weight-related comorbidities but without diabetes. The STEP-4 trial included a similar population, although patients were exposed to 20 weeks of semaglutide prior to randomisation and therefore had lower baseline BMI values and other weight-related biomarkers.

- 6.11 The STEP-2 trial included patients with diabetes who were overweight/obese and selected an older population (mean age 55 or 56 years) of predominantly white or Asian patients, with a balanced gender distribution and a lower baseline BMI but a higher incidence of weight-related comorbidities compared to the non-diabetes trial populations.
- 6.12 The ESC noted that all patients in the STEP clinical trial program received adjunctive behavioural therapy in addition to pharmacologic treatment. In the STEP-1, STEP-2, STEP-4 and STEP-5 trials this consisted of advice to reduce dietary intake by 500 kcal per day compared to baseline and to undertake at least 150 minutes of physical activity per week. Patients were also instructed to record their food intake and physical activity daily (via paper diary, app or similar tool) to assist and evaluate their lifestyle intervention. Counselling was administered by a dietician (or similar health care professional) every 4 weeks via visits or phone contacts.
- 6.13 Patients in the STEP-3 trial received more intensive behavioural therapy consisting of a low-calorie diet (1,000-1,200 kcal/day; using meal replacements) for the first 8 weeks before transitioning to a hypo-caloric diet (1,200-1800 kcal/day; using conventional foods) for the remainder of the 68-week trial. Patients were initially prescribed 100 minutes of physical activity per week which increased by 25 minutes every 4 weeks to reach a target of at least 200 minutes per week. Patients were also instructed to record their food intake and physical activity daily (via paper diary, app or similar tool) to assist and evaluate their lifestyle intervention. Counselling was administered during 30 individual behavioural therapy visits by a dietician (or similar health care professional).

### ***Comparative effectiveness***

- 6.14 The co-primary outcomes of the clinical evidence base were the mean change in body weight over time and the proportion of patients achieving > 5% weight loss from baseline. The submission claimed that a reduction in body weight of at least 5% over an observation period of at least 1 year is widely accepted as a clinically important change that is likely to lead to reductions in the risk of downstream complications such as diabetes, cardiovascular disease, osteoarthritis, gastro-oesophageal reflux disease, obstructive sleep apnoea, non-alcoholic steatohepatitis, urinary incontinence, polycystic ovary syndrome and some cancers. The ESC advised that the quantification of the impact of weight loss on the risk of downstream complications remains highly uncertain, especially if the treatment were used intermittently. The PBAC had previously raised concerns regarding the lack of long-term data supporting reductions in downstream complications for treatments claiming weight loss benefits

(semaglutide November 2019 Public Summary Document (PSD); exenatide July 2007 and November 2008 PSDs; sibutramine November 2006 and March 2008 PSDs).

6.15 Table 4 below summarises the change in body weight with semaglutide 2.4 mg and placebo in the STEP clinical trial program.

**Table 4: Change in body weight over time in the STEP trials with semaglutide 2.4 mg and placebo**

Outcome	Semaglutide 2.4 mg			Placebo			Treatment difference (95% CI)
	Baseline	Final	Mean change	Baseline	Final	Mean change	
<b>STEP-1 (baseline: Week 0, final: Week 68)</b>							
N	1,306	1,212	-	655	577	-	<b>-12.44%</b> <b>(-13.37; -11.51)</b>
Mean (SD) weight, kg	105.4 (22.1)	89.0 (22.7)	-13.7% (10.1)	105.2 (21.5)	101.9 (22.0)	-2.5% (7.4)	
<b>STEP-1 EXTENSION; OFF TREATMENT (baseline: Week 68, final: Week 120)</b>							
N	228	197	-	99	93	-	NR
Mean (SD) weight, kg	87.5 (21.4)	99.0 (22.5)	14.8% (10.7)	103.2 (25.6)	105.5 (26.2)	2.1% (4.9)	
<b>STEP-2 (baseline: Week 0, final: Week 68)</b>							
N	404	388	-	403	376	-	<b>-6.21%</b> <b>(-7.28; -5.15)</b>
Mean (SD) weight, kg	99.9 (22.5)	89.6 (21.0)	-9.9% (8.0)	100.5 (20.9)	96.8 (20.3)	-3.3% (5.5)	
<b>STEP-3 (baseline: Week 0, final: Week 68)</b>							
N	407	373	-	204	189	-	<b>-10.27%</b> <b>(-11.97; -8.57)</b>
Mean (SD) weight, kg	106.9 (22.8)	88.4 (21.5)	-16.5% (10.1)	103.7 (22.9)	98.3 (23.6)	-5.8% (7.7)	
<b>STEP-4 (baseline: Week 20, final: Week 68) [All patients received semaglutide for first 20 weeks]</b>							
N	535	520	-	268	250	-	<b>-14.75%</b> <b>(-16.00; -13.50)</b>
Mean (SD) weight, kg	96.5 (22.5)	89.0 (24.5)	-8.3% (-8.1)	95.4 (22.7)	100.6 (22.7)	6.5% (7.7)	
<b>STEP-5 (baseline: Week 0, final: Week 104)</b>							
N	152	144	-	152	128	-	<b>-12.55%</b> <b>(-15.33; -9.77)</b>
Mean (SD) weight, kg	105.6 (20.8)	91.4 (22.8)	-15.9% (12.3)	106.5 (23.1)	103.4 (20.9)	-1.9% (8.9)	

Source: Table 2-23 (p 82), Table 2-24 (p 85), Table 2-25 (p 88), Table 2-26 (p 90), Section 2.5.1.1.2 (p 84) of the submission

Abbreviations: CI, confidence interval; NR, not reported; SD, standard deviation

**Bold=statistically significant**

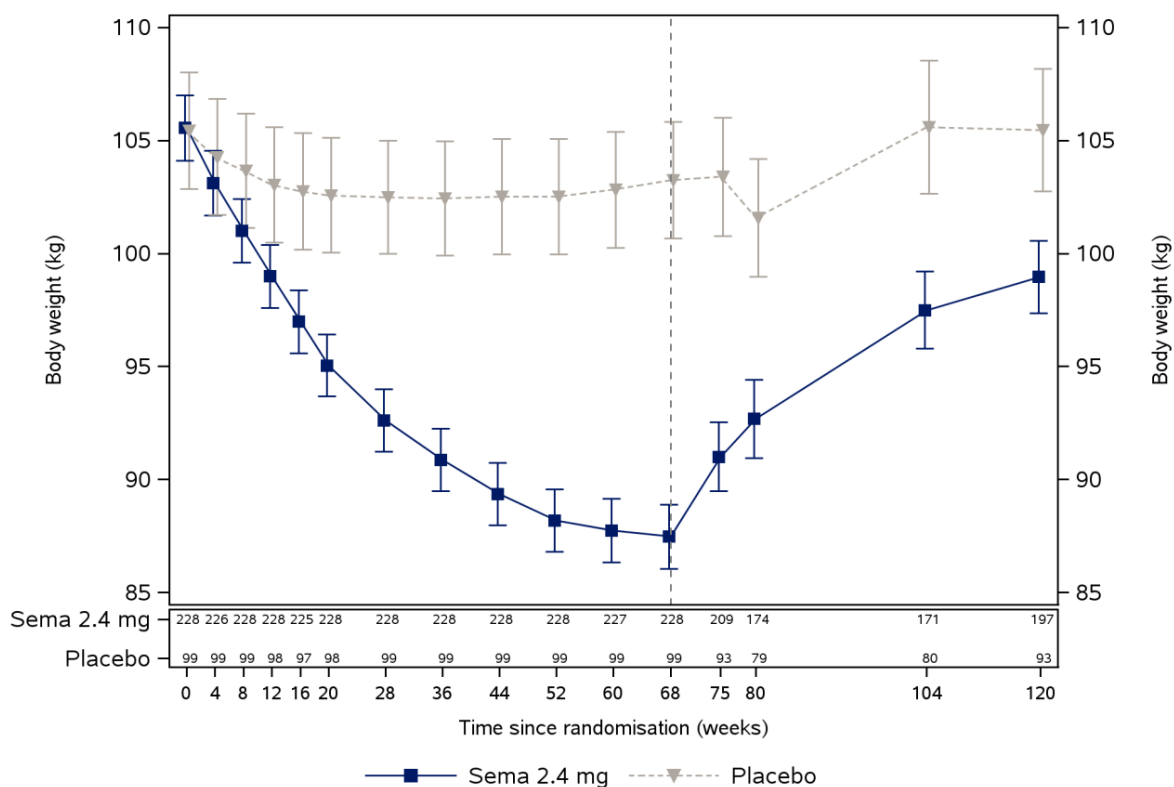
6.16 Treatment with semaglutide 2.4 mg was associated with a statistically significant reduction in body weight over time, with a treatment difference of between 10-13% compared to placebo in non-diabetic patients with and without adjunctive intensive behavioural therapy (STEP-1, STEP-3, STEP-5).

6.17 Treatment with semaglutide 2.4 mg was associated with smaller weight reductions in diabetic patients, with a treatment difference of 6% compared to placebo (STEP-2). The higher 2.4 mg dose of semaglutide was also associated with greater weight loss compared to the conventional 1.0 mg dose strength (treatment difference -2.65%; 95% CI -3.66, -1.64).

6.18 The reductions in body weight appeared to be maintained for two years while patients remained on treatment (STEP-5). Discontinuation of semaglutide treatment was

associated with an increase in body weight (STEP-1 extension, STEP-4), with a substantial proportion of initial reductions lost within a year (as shown in Figure 1 below for STEP-1 extension study).

Figure 1: Change in body weight over time with and without treatment in the STEP-1 extension study



Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean. Treatment arms refer to the main phase of the trial.  
 Source: Figure 14.2.9 (p 137) of the STEP-1 extension report

6.19 The proportions of patients achieving a 5%, 10%, 15% or 20% reduction in body weight with semaglutide 2.4 mg and placebo in the STEP clinical trial program are summarised in Table 5 below.

Table 5: Proportion of patients with weight loss in the STEP trials with semaglutide 2.4 mg and placebo

Study	Semaglutide 2.4 mg n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)
<b>Body weight loss of ≥5%</b>			
STEP-1 (68 weeks)	1047/1212 (86.4%)	182/577 (31.5%)	<b>11.22 (8.88, 14.19)</b>
STEP-2 (68 weeks)	267/388 (68.8%)	107/376 (28.5%)	<b>4.88 (3.58, 6.64)</b>
STEP-3 (68 weeks)	323/373 (86.6%)	90/189 (47.6%)	<b>6.11 (4.04, 9.26)</b>
STEP-5 (104 weeks)	111/144 (77.1%)	44/128 (34.4%)	<b>4.99 (2.95, 8.42)</b>
<b>Body weight loss of ≥10%</b>			
STEP-1 (68 weeks)	838/1212 (69.1%)	69/577 (12.0%)	<b>14.68 (11.08, 19.44)</b>
STEP-2 (68 weeks)	177/388 (45.6%)	31/376 (8.2%)	<b>7.41 (4.89, 11.24)</b>
STEP-3 (68 weeks)	281/373 (75.3%)	51/189 (27.0%)	<b>7.36 (4.93, 10.99)</b>
STEP-5 (104 weeks)	89/144 (61.8%)	17/128 (13.3%)	<b>7.23 (3.95, 13.23)</b>
<b>Body weight loss of ≥15%</b>			
STEP-1 (68 weeks)	612/1212 (50.5%)	28/577 (4.9%)	<b>19.26 (12.89, 28.76)</b>
STEP-2 (68 weeks)	100/388 (25.8%)	12/376 (3.2%)	<b>7.65 (4.11, 14.22)</b>
STEP-3 (68 weeks)	208/373 (55.8%)	25/189 (13.2%)	<b>7.87 (4.90, 12.63)</b>
STEP-5 (104 weeks)	75/144 (52.1%)	9/128 (7.0%)	<b>9.40 (4.41, 20.04)</b>
<b>Body weight loss of ≥20%</b>			
STEP-1 (68 weeks)	388/1212 (32.0%)	10/577 (1.7%)	<b>26.89 (14.18, 50.96)</b>
STEP-2 (68 weeks)	51/388 (13.1%)	6/376 (1.6%)	<b>6.84 (2.86, 16.33)</b>
STEP-3 (68 weeks)	133/373 (35.7%)	7/189 (3.7%)	<b>13.73 (6.23, 30.29)</b>
STEP-5 (104 weeks)	52/144 (36.1%)	3/128 (2.3%)	<b>12.84 (3.94, 41.88)</b>

Source: Table 2-28 (p 96) of the submission

Abbreviations: CI, confidence interval

**Bold=statistically significant**

- 6.20 A larger proportion of patients achieved each weight loss threshold with semaglutide 2.4 mg compared to placebo in the STEP trials. The differences between treatment arms were statistically significant in all trials. However, the magnitude of effect appeared to vary substantially between trials which may have been due to differences in patient populations and/or intensity of background behavioural therapy. The PSCR noted that the heterogeneity of study design was intentional and considered that a consistently clinically meaningful weight loss was achieved in all populations/settings.
- 6.21 A larger proportion of patients achieved each weight loss threshold with semaglutide 2.4 mg compared to semaglutide 1.0 mg in diabetes patients, although the differences between arms were substantially smaller than observed for the placebo comparison.
- 6.22 Table 6 below summarises the change in HbA1c with semaglutide 2.4 mg and placebo in the STEP clinical trial program.

Table 6: Change in HbA1c over time in the STEP trials with semaglutide 2.4 mg and placebo

Outcome	Semaglutide 2.4 mg			Placebo			Treatment difference (95% CI)
	Baseline	Final	Mean change	Baseline	Final	Mean change	
<b>STEP-1 (baseline: Week 0, final: Week 68)</b>							
N	1,306	1,197	-	655	563	-	<b>-0.29</b> <b>(-0.32, -0.26)</b>
Mean (SD) HbA1c %	5.7 (0.3)	5.2 (0.3)	-0.5 (0.3)	5.7 (0.3)	5.6 (0.4)	-0.2 (0.3)	
<b>STEP-1 EXTENSION; OFF TREATMENT (baseline: Week 68, final: Week 120)</b>							
N	227	196	-	98	91	-	NR
Mean (SD) HbA1c %	5.2 (0.3)	5.6 (0.3)	0.4 (0.3)	5.5 (0.4)	5.7 (0.5)	0.1 (0.3)	
<b>STEP-2 (baseline: Week 0, final: Week 68)</b>							
N	404	381	-	403	374	-	<b>-1.23</b> <b>(-1.42, -1.05)</b>
Mean (SD) HbA1c %	8.1 (0.8)	6.4 (1.2)	-1.7 (1.2)	8.1 (0.8)	7.8 (1.3)	-0.3 (1.3)	
<b>STEP-3 (baseline: Week 0, final: Week 68)</b>							
N	407	369	-	204	184	-	<b>-0.24</b> <b>(-0.29, -0.19)</b>
Mean (SD) HbA1c %	5.7 (0.3)	5.2 (0.3)	-0.5 (0.3)	5.8 (0.3)	5.5 (0.3)	-0.3 (0.2)	
<b>STEP-4 (baseline: Week 20, final: Week 68) [All patients received semaglutide for first 20 weeks]</b>							
N	535	515	-	268	246	-	<b>-0.24</b> <b>(-0.29, -0.19)</b>
Mean (SD) HbA1c %	5.4 (0.3)	5.2 (0.3)	-0.2 (0.3)	5.4 (0.3)	5.5 (0.3)	0.1 (0.2)	
<b>STEP-5 (baseline: Week 0, final: Week 104)</b>							
N	152	141	-	152	122	-	<b>-0.33</b> <b>(-0.41, -0.25)</b>
Mean (SD) HbA1c %	5.7 (0.3)	5.3 (0.3)	-0.5 (0.3)	5.7 (0.4)	5.6 (0.4)	-0.1 (0.3)	

Source: Table 2-30 (p 99) of the submission; Section 11.4.1 (p 45) of the STEP-1 extension trial report

Abbreviations: CI, confidence interval; NR, not reported; SD, standard deviation

**Bold=statistically significant**

- 6.23 Treatment with semaglutide 2.4 mg was associated with a reduction in HbA1c over time, with a treatment difference of approximately -0.3% compared to placebo in non-diabetic patients with and without adjunctive intensive behavioural therapy (STEP-1, STEP-3, STEP-5). The reductions in HbA1c appeared to be maintained for two years while patients remained on treatment (STEP-5). Discontinuation of semaglutide treatment was associated with an increase in HbA1c levels (STEP-1 extension, STEP-4), with a substantial proportion of initial reductions lost within a year. Treatment with semaglutide 2.4 mg was associated with larger HbA1c reductions in diabetic patients, with a treatment difference of approximately -1.2% compared to placebo (STEP-2). The change in HbA1c from baseline was similar for both the 2.4 mg and 1.0 mg semaglutide dose strengths (treatment difference -0.15%; 95% CI -0.34, 0.04).
- 6.24 The STEP clinical trials also demonstrated improvements in other measures of body weight, glucose metabolism, lipid profiles and blood pressure with semaglutide 2.4 mg compared to placebo. These differences appeared to be maintained while patients received therapy for up to two years but diminished after treatment cessation. Additionally, results generally favoured semaglutide 2.4 mg compared to semaglutide 1.0 mg in patients with diabetes.
- 6.25 No pre-specified subgroup analyses were identified in any of the included trial reports. However, a recently published abstract of the STEP-1 trial reported *post hoc* subgroup analyses for weight loss responders and mean change in body weight by age, gender, race, baseline body weight, baseline BMI, baseline waist circumference and glycaemic status (Kushner 2021). The ESC noted these analyses indicated that treatment effects

were relatively consistent for most subgroups, with the exception of gender and baseline body weight which were both likely to be treatment effect modifiers (interaction testing  $p < 0.001$ ). Reported weight loss was greater in females and patients with lower baseline body weight. The subgroup analyses could not be adequately evaluated given the limited detail available in the published abstract (these analyses were not provided in the submission). The PSCR provided additional data on *post hoc* subgroup analyses from the STEP-1 trial that had been previously published in abstract form (Kushner 2021). This data was from a conference presentation at the 2021 European Congress on Obesity. The presentation noted that, although not adjusted for multiplicity, female sex, being white, having a lower baseline body weight, and having normo-glycaemia were associated with a slightly greater response to semaglutide. The largest differences were associated with gender (estimated treatment difference in mean body weight for females: 16.3%, males: 9.4%) and baseline body weight (estimated treatment difference in mean body weight for patients weighing  $< 115$  kg: 15.2-16.4%, patients weighing  $> 115$  kg: 10.8%).

- 6.26 The submission presented *post hoc* analyses of weight reduction (change in weight over time and the proportion of patients achieving  $> 5\%$  weight loss from baseline) in the STEP-1 trial based on subgroups defined by baseline BMI and number of weight-related comorbidities. These analyses were poorly documented in the submission and additional data needed to be extracted during the evaluation (from the STEP-1 subgroup analyses statistical report and from individual patient data included in the economic model) to inform patient/disease characteristics as well as results. The submission did not provide any descriptive data on the outcomes in each treatment arm (e.g. mean baseline, final or observed change in weight). Additionally, the subgroup populations were not mutually exclusive and shared patients between groups may artificially minimise differences between populations. The submission also did not consider changes in other relevant biomarkers (HbA1c, systolic blood pressure, total cholesterol, HDL cholesterol) which were used in the economic model. Based on the submission's analyses (shown in Table 7 below), it claimed that the relative reductions in body weight with semaglutide treatment were consistent across subgroups defined by baseline BMI and weight-related comorbidities.

**Table 7: Comparison of co-primary body weight outcomes across subgroups in the STEP-1 trial**

Subgroup	N	Mean weight change from baseline Estimated treatment difference (95% CI)	$\geq 5\%$ reduction in weight Odds Ratio (95% CI)
ITT population	1,961	-12.44% (-13.37, -11.51)	11.22 (8.88, 14.19)
BMI $\geq 30$	1,844	-12.48% (-13.43, -11.52)	11.40 (8.95, 14.54)
BMI $\geq 30$ & $\geq 1$ comorbidity	1,412	-12.57% (-13.61, -11.53)	12.98 (9.81, 17.17)
BMI $\geq 30$ & $\geq 2$ comorbidity	955	-12.42% (-13.68, -11.16)	14.78 (10.45, 20.90)
BMI $\geq 35$	1,201	-11.73% (-12.90, -10.55)	9.93 (7.38, 13.36)
BMI $\geq 35$ & $\geq 1$ comorbidity <sup>a</sup>	949	-11.79% (-13.06, -10.52)	10.48 (7.52, 14.59)
BMI $\geq 35$ & $\geq 2$ comorbidity	643	-11.80% (-13.34, -10.27)	11.64 (7.76, 17.46)
BMI $\geq 40$	587	-12.00% (-13.60, -10.41)	12.63 (8.17, 19.55)
BMI $\geq 40$ & $\geq 1$ comorbidity	468	-11.67% (-13.43, -9.92)	11.61 (7.22, 18.67)
BMI $\geq 40$ & $\geq 2$ comorbidity	304	-11.06% (-13.22, -8.90)	11.52 (6.41, 20.73)

Source: Table 2-71 (p 145) of the submission

<sup>a</sup> The subgroup used in the economic analysis.

**Bold=statistically significant**

6.27 Table 8 summarises the change in quality-of-life measures over time with semaglutide 2.4 mg and placebo in the STEP clinical trial program.

**Table 8: Change in quality-of-life measures over time in the STEP trials with semaglutide 2.4 mg and placebo**

Mean (SD) Quality of life measures	Semaglutide 2.4 mg			Placebo			Treatment difference (95% CI)
	Baseline	Final	Mean change	Baseline	Final	Mean change	
<b>STEP-1 (baseline: Week 0, final: Week 68)</b>							
SF-36 Physical component summary <sup>a</sup>	51.1 (7.3)	53.6 (7.3)	2.4 (6.7)	51.1 (7.9)	51.4 (8.7)	0.2 (7.1)	<b>1.96</b> <b>(1.31, 2.61)</b>
- Physical functioning subscore <sup>b</sup>	51.0 (6.9)	53.4 (6.8)	2.3 (6.6)	50.8 (7.9)	51.3 (8.4)	0.4 (7.4)	<b>1.80</b> <b>(1.18, 2.42)</b>
SF-36 mental component summary <sup>c</sup>	55.4 (5.7)	54.0 (7.2)	-1.5 (7.1)	55.5 (5.9)	53.4 (7.9)	-2.1 (7.7)	<b>0.92</b> <b>(0.10, 1.73)</b>
IWQOL-Lite-CT total score <sup>d</sup>	63.6 (21.2)	80.1 (17.6)	16.2 (17.8)	63.3 (20.9)	70.0 (21.9)	6.3 (16.8)	<b>10.02</b> <b>(8.42, 11.62)</b>
- Physical functioning subscore <sup>e</sup>	65.4 (24.0)	80.7 (20.5)	15.0 (21.6)	64.0 (24.4)	70.3 (25.4)	6.0 (21.1)	<b>9.43</b> <b>(7.50, 11.35)</b>
<b>STEP-2 (baseline: Week 0, final: Week 68)</b>							
SF-36 Physical component summary <sup>a</sup>	49.8 (8.2)	52.3 (7.9)	2.3 (7.2)	49.9 (8.0)	50.9 (8.3)	0.9 (6.6)	<b>1.14</b> <b>(0.08, 2.21)</b>
- Physical functioning subscore <sup>b</sup>	49.2 (8.8)	52.1 (7.9)	2.8 (7.7)	49.6 (8.3)	50.5 (9.0)	0.8 (7.0)	<b>1.52</b> <b>(0.44, 2.60)</b>
SF-36 mental component summary <sup>c</sup>	55.6 (6.1)	54.7 (6.9)	-0.9 (6.9)	56.2 (5.5)	54.5 (7.0)	-1.8 (7.6)	0.38 (-0.74, 1.51)
IWQOL-Lite-CT total score <sup>d</sup>	71.9 (20.9)	82.4 (17.8)	10.1 (15.9)	74.2 (19.2)	79.8 (18.2)	5.2 (15.5)	<b>3.57</b> <b>(1.21, 5.93)</b>
- Physical functioning subscore <sup>e</sup>	67.1 (25.2)	79.0 (23.3)	11.4 (20.8)	69.2 (24.0)	75.3 (24.1)	4.9 (20.4)	<b>4.83</b> <b>(1.79, 7.86)</b>
<b>STEP-3 (baseline: Week 0, final: Week 68)</b>							
SF-36 Physical component summary <sup>a</sup>	51.6 (6.9)	54.6 (6.5)	3.2 (6.0)	51.7 (7.3)	54.1 (6.5)	2.6 (6.5)	0.69 (-0.54, 1.92)
- Physical functioning subscore <sup>b</sup>	51.9 (6.7)	54.2 (6.1)	2.5 (5.7)	52.1 (6.8)	53.7 (6.1)	1.7 (5.7)	0.84 (-0.23, 1.92)
SF-36 mental component summary <sup>c</sup>	55.7 (5.3)	54.8 (6.2)	-0.9 (6.0)	55.4 (6.1)	53.1 (8.9)	-2.2 (8.0)	<b>2.06</b> <b>(0.47, 3.64)</b>
<b>STEP-4 (baseline: Week 20, final: Week 68)</b>							
SF-36 Physical component summary <sup>a</sup>	54.3 (6.4)	55.2 (5.8)	0.8 (4.8)	54.4 (6.1)	53.6 (6.9)	-0.8 (5.5)	<b>1.68</b> <b>(0.64, 2.72)</b>
- Physical functioning subscore <sup>b</sup>	53.8 (5.7)	54.8 (4.8)	1.0 (3.8)	54.1 (5.0)	52.9 (6.6)	-1.2 (4.5)	<b>2.45</b> <b>(1.59, 3.32)</b>
SF-36 mental component summary <sup>c</sup>	55.0 (6.2)	55.1 (5.9)	0.0 (6.2)	54.9 (6.2)	52.5 (9.8)	-2.4 (8.5)	<b>3.44</b> <b>(2.28, 4.60)</b>

Source: Table 2-34 (p 105), Table 2-37 (p 106) of the submission; Section 11.5.1 (p 112-117), 11.5.2 (p 117-122) of the STEP-1 trial report; Section 11.6.1 (p 122-128), Section 11.6.2 (p 128-133) of the STEP-2 trial report; Section 11.6.1 (p 101-104) of the STEP-3 trial report; Section 11.5.1 (p 102-106) of the STEP-4 trial report

<sup>a</sup> SF-36 Physical component summary scores range from 6.11 to 79.67; higher scores indicate better quality of life

<sup>b</sup> SF-36 Physical functioning scores range from 19.03 to 57.60; higher scores indicate better quality of life

<sup>c</sup> SF-36 Mental component summary scores range from -3.83 to 78.75; higher scores indicate better quality of life

<sup>d</sup> IWQOL-Lite Total scores range from 0 to 100; higher scores indicate better patient functioning

<sup>e</sup> IWQOL-Lite Physical functioning scores range from 0 to 100; higher scores indicate better patient functioning

**Bold=statistically significant**

- 6.28 Treatment with semaglutide 2.4 mg was associated with a statistically significant improvement in SF-36 and IWQOL-Lite-CT physical functioning scores compared to placebo in both diabetic and non-diabetic patients (STEP-1, STEP-2), although larger benefits were observed in non-diabetic patients. SF-36 physical functioning scores also favoured semaglutide in patients receiving intensive behavioural therapy but the differences between treatment arms did not reach statistical significance (STEP-3). Discontinuation of semaglutide treatment was associated with a worsening of physical functioning scores back towards baseline levels (STEP-4).
- 6.29 Other quality-of-life outcomes also favoured semaglutide 2.4 mg compared to placebo although the differences were generally small between treatment arms and variable between trials.
- 6.30 There were no apparent differences in quality-of-life outcomes between different semaglutide dose strengths (2.4 mg or 1.0 mg) in diabetes patients.

### ***Comparative harms***

- 6.31 Treatment with semaglutide 2.4 mg was associated with an increased incidence and frequency of adverse events, treatment-related events, serious adverse events and adverse events leading to discontinuation compared to placebo in the STEP clinical trial program (see Table 9 below). Adverse events were more frequent during the initial titration phase but continued to occur throughout the treatment period.

Table 9: Overall summary of adverse events reported in the randomised trials

	STEP-1		STEP-2		STEP-3		STEP-4		STEP-5	
	SEMA 2.4	PBO	SEMA 2.4	PBO	SEMA 2.4	PBO	SEMA 2.4	PBO	SEMA 2.4	PBO
<b>Any adverse event</b>										
Incidence, n (%)	1,171 (90)	566 (86)	353 (88)	309 (77)	390 (96)	196 (96)	434 (81)	201 (75)	146 (96)	136 (90)
Events, n (rate per 100 years)	9,658 (566)	3,302 (398)	2,197 (412)	1,388 (263)	4,035 (767)	1,325 (507)	1,885 (346)	779 (293)	1,606 (532)	1,004 (375)
<b>Probably-related adverse event</b>										
Incidence, n (%)	571 (44)	147 (22)	169 (42)	62 (15)	183 (45)	44 (22)	125 (23)	29 (11)	96 (63)	48 (32)
Events, n (rate per 100 years)	2,148 (126)	330 (40)	456 (86)	100 (19)	694 (132)	107 (41)	305 (56)	42 (16)	444 (147)	151 (56)
<b>Possibly-related adverse event</b>										
Incidence, n (%)	726 (56)	223 (34)	182 (45)	93 (23)	284 (70)	98 (48)	179 (34)	50 (19)	91 (60)	50 (33)
Events, n (rate per 100 years)	2,700 (158)	555 (67)	534 (100)	170 (32)	1,262 (240)	216 (83)	367 (67)	91 (34)	290 (96)	116 (43)
<b>Serious adverse events</b>										
Incidence, n (%)	128 (10)	42 (6)	40 (10)	37 (9)	37 (9)	6 (3)	41 (8)	15 (6)	12 (8)	10 (12)
Events, n (rate per 100 years)	164 (10)	53 (6)	71 (13)	53 (10)	55 (11)	7 (3)	51 (9)	19 (7)	18 (6)	20 (8)
<b>Discontinuations due to adverse event</b>										
Incidence, n (%)	92 (7)	20 (3)	25 (6)	14 (4)	24 (6)	6 (3)	8 (2)	7 (3)	9 (6)	7 (5)
Events, n (rate per 100 years)	123 (7)	23 (3)	34 (6)	18 (3)	34 (7)	6 (2)	9 (2)	10 (4)	12 (4)	8 (3)

Source: Table 2-39 (p 109), Figure 2-34 (p 110), Table 2-43 (p 113), Figure 2-35 (p 115), Table 2-49 (p 119), Figure 2-36 (p 120), Table 2-56 (p 124), Figure 2-37 (p 125), Table 2-62 (p 129), Table 2-63 (p 131), Table 2-64 (p 133) of the submission

Abbreviations: NR, not reported; PBO, placebo; SEMA, semaglutide

- 6.32 Frequent adverse events (>5% of subjects) that occurred more often in the semaglutide 2.4 mg arm included nausea, diarrhoea, constipation, vomiting, abdominal pain, dyspepsia, abdominal pain upper, eructation, abdominal distension, flatulence, gastroenteritis, decreased appetite, headache, dizziness, and fatigue. Infrequent adverse events (>2% but <5%) that occurred more often in the semaglutide 2.4 mg arm included gastroesophageal reflux disease, abdominal discomfort, gastritis, viral gastroenteritis, alopecia and migraine. A similar pattern of events was observed for treatment-related events, serious adverse events and adverse events leading to discontinuation.
- 6.33 Treatment with semaglutide 2.4 mg was also associated with substantially higher use of concomitant medications for gastrointestinal events including drugs for acid-related disorders (e.g. proton pump inhibitors), functional gastrointestinal disorders (e.g. propulsives), diarrhoea (e.g. anti-propulsives), constipation (e.g. osmotically acting laxatives), anti-emetics and anti-nauseants (e.g. serotonin antagonists).

- 6.34 The higher 2.4 mg dose of semaglutide was also associated with more adverse events compared to the conventional 1.0 mg dose strength in the STEP-2 trial. The ESC noted that the pattern of adverse events was similar for both dose strengths (predominantly gastrointestinal and nervous system disorders).
- 6.35 The ESC considered the persistent and sometimes serious gastrointestinal adverse events may contribute to patients' intermittent use of semaglutide, which would diminish the potential long-term health benefits as weight loss and biomarker improvements are only maintained whilst on treatment.

### **Benefits/harms**

- 6.36 Based on the STEP-1 trial, for every 100 patients with overweight/obesity and without diabetes who were treated with semaglutide 2.4 mg in comparison with placebo over 68 weeks:
- There would be 55 additional patients who experience  $\geq 5\%$  weight loss, and of these 30 would experience weight loss of  $\geq 20\%$  (see Table 5, difference in proportions at 68 weeks).
  - There would be 168 additional adverse events (predominantly gastrointestinal events such as nausea, diarrhoea, vomiting, constipation and nervous system events such as headache) and 4 additional serious adverse events requiring hospitalisation (see Table 9 above, difference in event rates).
- 6.37 There were insufficient data to adequately assess the comparative benefits and harms of semaglutide in the target subgroup population of the STEP-1 trial (BMI  $\geq 35$  kg/m<sup>2</sup> with at least one weight-related comorbidity).
- 6.38 Based on the STEP-2 trial, for every 100 patients with overweight/obesity and diabetes who were treated with semaglutide 2.4 mg in comparison with placebo over 68 weeks:
- There would be 40 additional patients who experience  $\geq 5\%$  weight loss, and of these 12 would experience weight loss of  $\geq 20\%$  (see Table 5, difference in proportions at 68 weeks).
  - There would be 149 additional adverse events (predominantly gastrointestinal events such as nausea, diarrhoea, vomiting, constipation and nervous system events such as headache) and 3 additional serious adverse events requiring hospitalisation (see Table 9 above, difference in event rates).

### **Clinical claim**

- 6.39 The submission described semaglutide 2.4 mg as superior in terms of effectiveness and inferior in terms of safety compared to placebo. The ESC advised that the STEP trial program demonstrated efficacy of semaglutide in leading to weight loss, but that this benefit appeared to revert after treatment cessation. Although there were no new safety signals, it was unclear how much of the weight loss was due to nausea, satiety

or favourable metabolic effects. The ESC also noted that the following issues should be considered:

- The lack of long-term data demonstrating a reduction in the downstream complications of obesity as well as limited long-term data to support the safety of the new higher dose of semaglutide for obesity.
- The applicability of the trial outcomes to clinical practice given the potential for differences in patient populations (e.g. proportion of males and females with severe obesity) and circumstances of use (e.g. suboptimal compliance, intermittent courses of therapy). The PSCR considered that semaglutide would have similarly strong uptake in practice among females as was seen in the trials. It noted that data from a liraglutide patient support program indicated that 79% of this (private) market was female, and the Australian Bariatric Services Registry showed that females represented 78.6% of those who had a bariatric procedure (ABSR 2019).
- Whether outcomes would be realised in practice, given that treatment was intended as adjunct to diet and exercise but the role of the multidisciplinary care team was poorly defined in the submission, and given that access to diet and exercise counselling was likely more limited in the Australian setting than was available in the trial.

6.40 Overall, the ESC considered it was likely that, given the cyclical nature of weight loss and gain, and the adverse event profile, patients were likely to receive multiple cycles of semaglutide therapy rather than remain on therapy over a longer continuous treatment duration. This added further uncertainty to the magnitude of potential long-term health gains.

6.41 The PBAC considered that the claim of superior comparative effectiveness was reasonable for weight loss, HbA1c and other biomarkers, and quality of life over the trial duration and whilst on treatment, although it was unlikely that these benefits would be fully realised in Australian practice without the intensive diet and exercise counselling co-administered in the trial program. These benefits would also likely be diminished if semaglutide were used intermittently. Moreover, despite the favourable effects on the short-term and surrogate outcomes the clinical effectiveness on clinical endpoints remained uncertain.

6.42 The PBAC considered the inferior comparative safety claim was reasonable. Notably, the PBAC agreed with the ESC that these adverse events would contribute to intermittent use of semaglutide outside of a trial setting.

### ***Economic analysis***

6.43 The submission presented a modelled economic evaluation of semaglutide compared to placebo for the treatment of severe obesity. The economic evaluation was based predominantly on a subgroup analysis of the STEP-1 trial with additional modelled

data using multiple risk equations. The economic evaluation was presented as a cost-utility analysis.

- 6.44 No economic analysis was presented for the use of semaglutide in diabetic patients with severe obesity.
- 6.45 The evaluation of the economic analysis was hindered by the lack of documentation for many of the data sources, assumptions, calculations and values used in the economic model. As such, many of the estimates presented in the submission could not be validated during the evaluation.

**Table 10: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years
Time horizon	20 years
Methods used to generate results	Individual patient-level microsimulation model
Treatments	Semaglutide; placebo
Health states	10 health states: normoglycaemia, prediabetes, diabetes, normoglycaemia with history of myocardial infarction/unstable angina, normoglycaemia with history of stroke, normoglycaemia with history of myocardial infarction/unstable angina and stroke, pre-diabetes/diabetes with history of myocardial infarction/unstable angina, pre-diabetes/diabetes with history of stroke, pre-diabetes/diabetes with history of myocardial infarction/unstable angina and stroke; death
Cycle length	Quarterly cycles for first 2 years then annual cycles for subsequent years
Transition probabilities	<p>Change in biomarkers (BMI, HbA1c, systolic blood pressure, total cholesterol, HDL-cholesterol) for the first 6 cycles of the model were based on individual patient data from the STEP-1 target subgroup population. The model assumed that BMI values at the end of the trial (68 weeks) would be maintained over time while patients remain on treatment. The model estimated weight regain after treatment discontinuation based on data from the STEP-4 withdrawal trial. The model assumed that other biomarkers remained constant at their final 68 week value for the remainder of the model (up to 20 years) with no adjustment for treatment discontinuation.</p> <p>The risk of adverse events was based on the reported frequency of serious gastrointestinal events reported in the overall population of the STEP-1 trial.</p> <p>The risk of treatment discontinuation was based on aggregate data from the STEP-1 target subgroup population for the first 6 cycles of the model with retrospective application of proposed continuation rules (<math>\geq 5\%</math> weight loss at 28 weeks; <math>\geq 10\%</math> weight loss at 52 weeks). Discontinuation beyond this period was based on an arbitrary assumption.</p> <p>Biomarker changes as well as other patient characteristics were used to inform risk equations for diabetes (QDiabetes), incident cardiovascular events in non-diabetics (QRisk3), recurrent cardiovascular events in non-diabetics (Framingham Heart) and incident and recurrent cardiovascular events in diabetics (UKPDS82).</p> <p>HbA1c levels were used to inform the risk of pre-diabetes (<math>\geq 5.7\%</math> HbA1c). BMI and other variables were used to inform the risk of obstructive sleep apnoea (Young 2002), bariatric surgery (Yates 2017) and knee surgery (Wendelboe 2003).</p> <p>Health state mortality was estimated based on Australian life tables with risk adjustments for patients with a history of myocardial infarction/unstable angina (Norgaard 2010) or a history of stroke (Brønnum-Hansen 2001)</p>

Component	Description
Utility values	<p>General population utility values were based on Australian estimates for healthy weight individuals (Norman 2013) with additional age-related disutility values (Søltøft 2009).</p> <p>Weight-based disutility values were not estimated from the clinical trial data but were estimated based on a cross-sectional survey of utility scores in patients awaiting bariatric surgery in Australia (Khan 2012).</p> <p>Health state disutility values for normoglycaemia and pre-diabetes were assumed. The submission used published sources to inform the disutility of diabetes health states (Gough 2009) as well as cardiovascular health states (Sullivan 2011). Health state disutility values were combined using an additive approach.</p> <p>Event disutility values were based on various published sources (Clarke 2002, Gough 2009, Sullivan 2011, Campbell 2010) and additional assumptions regarding the duration of events.</p> <p>The adverse event disutility value was assumed.</p>
Costs	<p>Semaglutide drugs costs were estimated based on the proposed effective price.</p> <p>The costs of weight management advice were based on MBS costs and the assumption that all patients in both arms would receive monthly dietician visits over the 20 year model duration.</p> <p>Costs for normoglycaemia and cardiovascular health states were assumed. The cost of pre-diabetes and diabetes was based on a costing study using data from the 2004-2005 Australian Diabetes, Obesity and Lifestyle study (Lee 2013).</p> <p>Costs for obstructive sleep apnoea were based a cost effectiveness study of continuous positive airway pressure treatment (CPAP) for obstructive sleep apnoea in the Australian setting (Streatfeild 2019). Other event costs were based on AR-DRG hospitalisation costs.</p> <p>Serious adverse event costs were based on AR-DRG hospitalisation costs. Non-serious adverse events were not costed.</p> <p>Costs estimated in the submission were inflated to 2021 values using the health sub-category of the consumer price index (CPI)</p>
Discount rate	█ % for costs and outcomes
Software package	Microsoft Excel

Source: Table 3-1 (p 163) of the submission

- 6.46 All patients begin the model with synthesised patient characteristics based on the STEP-1 target subgroup population as well as other data sources. Based on synthesised glycaemic status, modelled patients could start in either the normoglycaemia or pre-diabetes health state (patients could not start in the diabetes health state in the base case). Cardiometabolic risk factors (BMI, HbA1c, systolic blood pressure, total cholesterol, HDL-cholesterol) were allowed to change over the first 6 cycles (18 months) of the model based on individual patient data from the STEP-1 subgroup. After this point, cardiometabolic risk factors remain fixed for the duration of the model with the exception of BMI, which could return to baseline levels after treatment discontinuation.
- 6.47 During each cycle of the model, patients could remain on treatment or discontinue therapy, change glycaemic status (normoglycemia, prediabetes, diabetes; modelled

patients could only move between normoglycaemia and pre-diabetes during the first 18 months) and/or experience:

- no event,
- fatal/non-fatal myocardial infarction,
- fatal/non-fatal unstable angina,
- fatal/non-fatal stroke,
- transient ischemic attack,
- fatal/non-fatal knee surgery,
- fatal/non-fatal bariatric surgery,
- obstructive sleep apnoea,
- adverse event,
- death from other causes.

6.48 Patients could only experience one cardiovascular event per cycle but could experience multiple other modelled events. Glycaemic status and events occurring in each cycle were used to allocate patients to each of the health states. Health state allocation could then feedback into the risk calculations and influence the risk of experiencing a future event.

6.49 Overall, the ESC agreed with the evaluation that the economic model appeared to be unnecessarily complex primarily due to the complexity of modelling cardiovascular events and health states which only had a limited impact on the incremental differences between treatment arms. The ESC considered that the microsimulation approach was broadly reasonable, but that the economic model did not capture the impact of the likely cyclical nature of semaglutide treatment, in both responders and non-responders (as permitted by the requested restriction), which likely substantially overestimated the cost-effectiveness.

6.50 Key drivers of the economic model are summarised in Table 11 below.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact in base case
Residual treatment effects	<p>The model estimated weight regain after treatment discontinuation based on data from the STEP-4 withdrawal trial and assumed that patients would only regain weight up to their baseline BMI value. Data from the STEP-1 off-treatment extension study suggest that weight regain could be more rapid than observed in the STEP-4 withdrawal trial.</p> <p>The model assumed that other biomarkers (HbA1c, total cholesterol, HDL, systolic blood pressure) would remain constant at their final value in the STEP-1 trial (68 weeks) for the remainder of the model (up to 20 years) with no adjustment for treatment discontinuation. This assumption was inconsistent with the clinical data which indicated that biomarkers worsen towards baseline levels after treatment discontinuation. This assumption strongly biases the analysis in favour of semaglutide as it generates ongoing treatment benefits for semaglutide (particularly in terms of HbA1c, which substantially reduces the risk of pre-diabetes and diabetes) without the ongoing costs of treatment. The PSCR revised the base case, where it assumed that other biomarkers returned to baseline values after treatment discontinuation (see paragraph 6.61).</p>	High, favours semaglutide
Treatment persistence	<p>The submission estimated in-trial discontinuations based on aggregate data on the proportion of patients who had discontinued semaglutide treatment by Week 68 in the target subgroup population of the STEP-1 trial. The submission did not justify the use of aggregate data given the availability of individual patient data on discontinuations and given the approach was inconsistent with that used for other modelled variables from the STEP-1 trial.</p> <p>The proposed continuation rules (<math>\geq 5\%</math> reduction in body weight at 28 weeks and <math>\geq 10\%</math> reduction in body weight at 52 weeks) were retrospectively applied in the model at Cycle 2 (using Week 16 trial data) and Cycle 4 (using Week 44 trial data). The difference in timing between the proposed continuation rules and the trial data used in the economic model was not justified. Based on individual patient data for the target subgroup in the STEP-1 trial, 67.8% of patients would meet the 5% threshold at 16 weeks vs. 83.0% meeting the threshold at 28 weeks. Similarly, 61.1% of patients would meet the 10% threshold at 44 weeks vs. 63.5% meeting the threshold at 52 weeks. The PSCR acknowledged this as a programming error and the approach was revised in the PSCR base case (see paragraph 6.61).</p> <p>The estimation of treatment persistence based on in-trial discontinuations and treatment rules will lead to double counting. For example, a patient who discontinued the trial at Week 10 (for various reasons) would contribute to the in-trial discontinuation rate but may not achieve the target BMI thresholds and therefore also be counted as a discontinuation due to the treatment rules. The combined (in-trial discontinuation and continuation rules) modelled estimate of treatment persistence at 28 weeks (65.5%) and 52 weeks (49.0%) are substantially lower than the target subgroup population of the STEP-1 trial (83.2% at 68 weeks). The PSCR disputed that the approach led to double counting but noted that the sponsor was investigating options to improve the modelling of treatment discontinuations using patient level treatment persistence data.</p> <p>The modelled treatment persistence was also substantially lower than the estimated persistence in the estimated PBS usage and financial implications (71.2% at 52 weeks).</p> <p>The model assumed an annual 5% discontinuation rate after the trial period. No justification was provided for this assumption.</p>	High, favours semaglutide

Public Summary Document – March 2022 PBAC Meeting

Description	Method/Value	Impact in base case
Baseline utility values	<p>The submission estimated baseline age and gender of modelled patients based on individual patient data for each treatment arm from the target subgroup population of the STEP-1 trial.</p> <p>The submission estimated utility values of healthy weight males and females based on SF-36 data captured in the Household, Income and Labour Dynamics in Australia (HILDA) survey (Norman 2013). The submission then estimated age band utility values based on EQ-5D-3L data captured in the 2003 Health Survey for England (Søltøft 2009). The ESC considered it unclear why Australian norms had not also been used for age-related decline.</p> <p>The approach used in the submission was not appropriate as it resulted in substantial differences in quality-adjusted life years before treatment effects were applied due to differences between treatment arms in age/gender (baseline differences represented 24% of the overall difference in QALYs between treatment arms, and the impact on quality of life was larger than any other factor other than weight). This approach was revised in the PSCR base case, which included a single age and gender-neutral baseline utility value of 0.782, for subjects with BMI 18-24.9, as reported in Norman 2013 (see paragraph 6.61). The ESC considered this revised approach was more reasonable.</p>	High, favours semaglutide
Weight-based disutility	<p>The submission acknowledged that quality-of-life data were captured in the clinical trials but argued that SF-36 and IWQOL-Lite-CT are generic, insensitive and non-preference-based instruments and therefore are uninformative for determining weight-related disutility values. This argument may not be reasonable as SF-36 quality of life scores can be mapped to SF-6D utility values using established algorithms. Additionally, using data from the trials has significant advantages over other data sources as it provides longitudinal data based on individual patients changing weight over a short time duration. This potentially allows the analysis to capture the QALY gain associated with weight loss (which may not be the same as the QALY loss associated with weight gain) while minimising the confounding effects of other comorbidities. The pre-PBAC response noted that the sponsor had commissioned a <i>post hoc</i> analysis of transformed SF-6D utility scores from the STEP-1 trial. A complete report, including methods and results, will be provided in a resubmission and consideration given to how these data might best be applied to the economic evaluation.</p> <p>Instead of using trial data, the economic model estimated weight-related disutility values based on a cross-sectional survey assessing generic AQL-8D scores in patients awaiting bariatric surgery in Australia (Khan 2012; estimated disutility of -0.006 per BMI unit increase). An alternative Australian utility study was identified during the evaluation that assessed the impact of overweight and obesity on SF-6D scores using data from the Australian National Health Survey 1995 (Kortt 2005; -0.0024 in males and -0.0034 in females per BMI unit increase). The ESC noted that Kortt 2005 was based on the algorithm for the SF-6D, which it considered likely to underestimate the disutility, but ESC agreed with the evaluation that the weight-based disutilities were highly uncertain given the range of values in the literature and the lack of validation against the semaglutide trial data.</p>	High, favours semaglutide

Description	Method/Value	Impact in base case
Glycaemic health state costs	<p>The submission assumed that there were no costs associated with the normoglycaemia health state. This assumption was not consistent with the data source used to estimate pre-diabetes and diabetes costs which suggested that patients with normoglycemia also have ongoing healthcare costs.</p> <p>The submission estimated pre-diabetes and diabetes health state costs based on a costing study of diabetes using data from the 2004-2005 Australian Diabetes, Obesity and Lifestyle study (Lee 2013). This study provided average annual healthcare cost estimates for patients with normoglycaemia, impaired fasting glucose, impaired glucose tolerance and diabetes by complication status (none, microvascular, macrovascular, both microvascular and macrovascular).</p> <p>The submission estimated the cost of pre-diabetes based on the average weighted cost of patients with impaired fasting glucose and impaired glucose tolerance. However, the costs of patients with normoglycaemia should have been subtracted from the average cost of patients with pre-diabetes in order to estimate the incremental costs associated with pre-diabetes (this was noted in the text of the Excel model but was not incorporated into the calculation). This adjustment is necessary to align the pre-diabetes cost estimates with the assumption of no costs for normoglycaemia (submission estimate of pre-diabetes annual cost: \$3,422 vs adjusted result of \$415).</p> <p>The submission estimated the cost of diabetes based on the average weighted cost of patients with diabetes and no complication as well as patients with diabetes and microvascular complications. The exclusion of macrovascular costs was appropriate as these costs are already captured in other parts of the model. The costs of patients with normoglycaemia should have been subtracted from the average cost of patients with diabetes in order to estimate the incremental costs associated with diabetes. This adjustment is necessary to align the diabetes cost estimates with the assumption of no costs for normoglycemia (submission estimate of diabetes annual cost \$5,072 vs. adjusted estimate of \$1,569).</p> <p>In its revised base case, the PSCR modified the estimated health state costs for pre-diabetes and diabetes to reflect the incremental difference over the normoglycaemia state (see paragraph 6.61). However, the PSCR considered the revised costs to be considerable underestimates. The ESC noted the costing study was old, but considered the source was appropriate.</p>	High, favours semaglutide

Source: Constructed during the evaluation

- 6.51 A substantial number of calculation errors, logical inconsistencies and unsupported values throughout the submission were identified during the evaluation. There were also a number of additional issues with the economic model (use of hybrid health states, lack of biomarker drift reflecting natural progression, synthesised patient characteristics from multiple sources, limited data to inform circumstances of use, validity of risk equations, minimising the impact of adverse events, use of additive utility values, uncertain event durations for disutility values and use of CPI inflation factors) that were further described in the commentary.
- 6.52 The incremental difference in costs for healthcare resource items used in the economic evaluation is summarised in Table 12 below.

**Table 12: Healthcare resource items: disaggregated summary of cost impacts (discounted)**

Type of resource item	Semaglutide	Placebo	Incremental cost
<b>Intervention costs</b>			
Drug costs	\$█	\$0	\$█
Weight management costs	\$8,931	\$8,911	\$19
<b>Event costs</b>			
Myocardial infarction	\$88	\$111	-\$22
Unstable angina	\$1,348	\$1,614	-\$266
Stroke	\$151	\$157	-\$6
Transient ischaemic attack	\$0.50	\$0.78	-\$0.29
Obstructive sleep apnoea	\$2,200	\$2,532	-\$332
Knee surgery	\$2,390	\$2,965	-\$575
Bariatric surgery	\$395	\$423	-\$28
Adverse event	\$482	\$0	\$482
<b>Health state costs</b>			
Normoglycaemia	\$0	\$0	\$0
Pre-diabetes	\$4,049	\$14,242	-\$10,193
Diabetes	\$3,495	\$6,159	-\$2,664
Normoglycaemia with history of myocardial infarction/unstable angina	\$340	\$257	\$83
Normoglycaemia with history of stroke	\$17.50	\$9.97	\$7.52
Normoglycaemia with history of myocardial infarction/unstable angina and stroke	\$6.46	\$6.58	-\$0.13
Pre-diabetes/diabetes with history of myocardial infarction/unstable angina	\$506	\$1,622	-\$1,116
Pre-diabetes/diabetes with history of stroke	\$46	\$86	-\$40
Pre-diabetes/diabetes with history of myocardial infarction/unstable angina and stroke	\$7	\$35	-\$28
<b>Hybrid health states cost allocation breakdown</b>			
- Pre-diabetes/diabetes	\$466	\$1,749	-\$1,184
- Cardiovascular	\$99	\$298	-\$198
<b>Total costs</b>	<b>\$█</b>	<b>\$39,130</b>	<b>\$█</b>

Source: Table 3-8 (p 189) of the submission and Section 3 Workbook.xlsm

Note: There was an error in the Excel spreadsheet calculating disaggregated outcomes; hybrid health states and adverse event estimates were based on the last model run rather than the average across all 10 model runs. This error was corrected during the evaluation. The redacted values correspond to the following ranges:

- 6.53 The difference in total cost between treatment arms was driven by semaglutide drug costs which was largely offset by downstream reduced incidence and costs associated with the development of pre-diabetes and diabetes.
- 6.54 The incremental difference in health outcomes estimated in the economic evaluation is summarised in Table 13 below. The ESC considered that these appeared optimistic.

**Table 13: Summary of health outcomes included in the economic evaluation**

Health outcome	Semaglutide	Placebo	Incremental difference
<b>Events per 1,000 patients</b>			
Non-fatal myocardial infarction	5.8	8.0	-2.2
Fatal myocardial infarction	0.2	0.2	0
Non-fatal unstable angina	117.9	140.5	-22.6
Fatal unstable angina	4.3	4.5	-0.2
Non-fatal stroke	10.2	11.5	-1.3
Fatal stroke	1.3	1.1	0.2
Transient ischaemic attack	0.3	0.5	-0.2
Obstructive sleep apnoea (each year spent with the condition counted as a single event)	8,059.9	9,209.1	-1,150.1
Non-fatal knee surgery	200.3	241.0	-40.6
Fatal knee surgery	2.7	2.6	0.2
Non-fatal bariatric surgery	49.0	52.6	-3.7
Fatal bariatric surgery	0.6	0.5	0.2
Adverse events	272.5	0	272.5
<b>QALYs (discounted)</b>			
Persons with healthy weight	9.6026	9.6026	0.0000
Decrement for patient demographics (age, gender) and non-cardiovascular mortality <sup>a</sup>	-0.7643	-0.8227	0.0585
Decrement for cardiovascular and surgical mortality <sup>b</sup>	-0.2296	-0.2281	0.0016
Decrement for weight-related disutility	-0.9424	-1.0859	0.1435
Decrement for normoglycaemia (all relevant states)	0.0000	0.0000	0.0000
Decrement for pre-diabetes (all relevant states)	0.0000	0.0000	0.0000
Decrement for diabetes (all relevant states)	-0.0226	-0.0435	0.0208
Decrement for cardiovascular events (MI, UA, stroke, TIA)	-0.0097	-0.0115	0.0018
Decrement for history of cardiovascular disease (all relevant states)	-0.0167	-0.0206	0.0039
Decrement for obstructive sleep apnoea	-0.0577	-0.0664	0.0087
Decrement for knee surgery	-0.0196	-0.0241	0.0046
Decrement for bariatric surgery	-0.0051	-0.0054	0.0004
Decrement for adverse events	-0.0001	0.0000	-0.0001
<b>Total QALYs</b>	<b>7.5348</b>	<b>7.2942</b>	<b>0.2405</b>

Source: Table 3-8 (p 189) of the submission, and Section 3 Workbook.xlsm

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; QALY, quality adjusted life years; TIA, transient ischemic attack; UA, unstable angina

<sup>a</sup> Risk multipliers applied to post ACS and post-stroke health states were excluded from this analysis

<sup>b</sup> Risk multipliers applied to post ACS and post-stroke health states were included in this analysis

Note: There was an error in the Excel spreadsheet calculating disaggregated outcomes; hybrid health states and adverse event estimates were based on the last model run rather than the average across all 10 model runs. This error was corrected during the evaluation

6.55 The difference in quality-adjusted life years (QALY) between treatment arms was primarily driven by weight-related disutility values. The disaggregated outcomes also revealed a substantial bias in favour of semaglutide, which was associated with better utility values prior to any treatment effects being applied due to differences in baseline demographics between treatments arms.

6.56 The results of the modelled economic evaluation are summarised in Table 14 below.

**Table 14: Results of the modelled economic evaluation**

Component	Semaglutide	Placebo	Increment
Costs (\$)		\$39,130	
QALYs	7.5348	7.2942	0.2405
<b>Incremental cost per QALY gained (\$)</b>			<b>1</b>

Source: Table 3-10 (p 190) of the submission

Abbreviations: QALY, quality adjusted life years

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

- 6.57 Based on the economic model, treatment with semaglutide was associated with an incremental cost per QALY gained of \$15,000 to < \$25,000 compared to placebo for the management of severe obesity. The ESC advised that the cost-effectiveness estimate should not be considered reliable given the poorly justified assumption regarding ongoing benefits after treatment cessation, the disconnect between observed and modelled discontinuation patterns, the baseline difference in utilities between treatment arms, the incorrect calculation of pre-diabetes/diabetes health state costs and the inadequate justification of weight-based disutility values. Moreover, the model did not capture the impact of the cyclical nature of treatment, in both responders and non-responders (as would be permitted under the restriction).
- 6.58 The results of the sensitivity analyses indicated that the model was most sensitive to treatment persistence, risks of prediabetes and diabetes as well as the costs of the prediabetes and diabetes health states.

Table 15: Results of sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
<b>Base case</b>		<b>0.2405</b>	<b>1</b>
<b>Discount rate (base case: % for benefits and costs)</b>			
% discount rate		0.2735	2
% discount rate		0.3831	2
<b>Time horizon (base case: 20 years)</b>			
10 years		0.1553	3
30 years		0.2689	2
<b>Patient population (base case: patients with &gt; 35 BMI with at least one comorbidity)</b>			
ITT population		0.2411	3
BMI ≥ 30 <sup>a</sup>		0.2442	3
BMI ≥ 30 & ≥ 1 comorbidity <sup>a</sup>		0.2476	1
BMI ≥ 30 & ≥ 2 comorbidity <sup>a</sup>		0.2359	1
BMI ≥ 35 <sup>a</sup>		0.2059	1
BMI ≥ 35 & ≥ 2 comorbidity <sup>a</sup>		0.2904	2
BMI ≥ 40 <sup>a</sup>		0.2080	1
BMI ≥ 40 & ≥ 1 comorbidity		0.2524	2
BMI ≥ 40 & ≥ 2 comorbidity <sup>a</sup>		0.2026	1
<b>Treatment compliance (base case: trial-based estimates from target population in STEP-1, continuation rules at Week 16 and Week 44, assumption of 5% annual discontinuation post-trial)</b>			
No continuation rules		0.2989	4
5% weight loss continuation rule applied at 28 weeks & 10% weight loss continuation rule applied at 52 weeks <sup>a</sup>		0.2663	1
Assumption of 0% annual discontinuation post-trial		0.3163	3
Assumption of 10% annual discontinuation post-trial		0.1919	5
<b>Biomarker treatment effects (base case: individual patient data for target population in STEP-1)</b>			
Remove HbA1c treatment effects (assume all timepoints same as baseline) <sup>a</sup>		0.2184	6
<b>Post-treatment effects (base case: BMI regained based on STEP-4 trial, other biomarkers remain constant)</b>			
BMI regain based on STEP-1 extension		0.2237	1
HbA1c regain 0.4 per year (STEP-1 extension) until equal to baseline <sup>a</sup>		0.2202	7
<b>Utility/disutility values (base case: various sources)</b>			
Remove age/gender difference in utility values (set baseline at 0.782 for all patients) <sup>a</sup>		0.2038	1
Decrease weight disutility by 50% (consistent with Kortt 2005 estimate)		0.1687	1
Increase weight disutility by 50%		0.3123	2
<b>Healthcare costs (base case: various sources)</b>			
Pre-diabetes and diabetes costs adjusted for normoglycaemia and AIHW health inflation index <sup>a</sup>		0.2405	7

Source: Table 3-12 (p 192) of the submission

<sup>a</sup> Added during evaluation

The redacted values correspond to the following ranges:

- 1 \$15,000 to < \$25,000
- 2 \$5,000 to < \$15,000
- 3 \$25,000 to < \$35,000
- 4 \$45,000 to < \$55,000
- 5 \$0 to < \$5,000
- 6 \$75,000 to < \$95,000
- 7 \$55,000 to < \$75,000

6.59 During the evaluation, a multivariate sensitivity analysis was conducted based on observed HbA1c regain, adjusted pre-diabetes and diabetes health state costs, removal of age/gender differences in underlying utilities and continuation rules based on appropriate time points. This analysis was further tested with an alternative estimate of weight-based disutility. An error in these calculations was identified and corrected in the ESC advice. Corrected results are shown in Table 16 below.

**Table 16: Results of multivariate sensitivity analyses**

Analyses	Incremental cost (\$)	Incremental QALY	ICER (\$)
<b>Base case</b>		<b>0.2405</b>	<b>█<sup>1</sup></b>
Multivariate analysis including observed HbA1c regain, adjusted pre-diabetes and diabetes health state costs, removal of age/gender differences in underlying utilities and continuation rules based on appropriate time points		0.2118	█ <sup>2</sup>
- Decrease weight disutility by 50% (consistent with Kortt 2005 estimate)		0.1283	█ <sup>3</sup>

Source: Constructed during the evaluation based on 'Section 3 Workbook' spreadsheet provided with the submission

The redacted values correspond to the following ranges:

<sup>1</sup> \$15,000 to < \$25,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$135,000 to < \$155,000

6.60 As already noted above, a substantial number of calculation errors, logical inconsistencies and unsupported values throughout the submission were identified during the evaluation. Given this, the ICERs presented in the submission should not be considered reliable. Multivariate analyses with input adjustments for unfounded assumptions and errors resulted in an increase from the base case ICER of \$15,000 to < \$25,000/QALY gained to between \$75,000 to < \$95,000 to \$135,000 to < \$155,000 per QALY gained.

6.61 The PSCR acknowledged a number of the issues identified in the evaluation (see Table 11) and presented an alternative base case of \$75,000 to < \$95,000 per QALY gained. The PSCR's revised base case included biomarkers returning to baseline values upon treatment discontinuation, correction of timepoint errors for implementing continuation rules, adoption of gender/age neutral baseline utility values and use of adjusted incremental pre-diabetes/diabetes health state costs. The updated analyses also made revisions with respect to some other smaller issues identified during the evaluation (incorrect distribution of cardiovascular events, inappropriate removal of diabetes mortality, sequential duplication of patients from the placebo arm). The ESC noted the impact on the ICER of these revisions and several of the sensitivity analyses showed the model was highly sensitive to multiple factors and long-term benefits modelled remained highly uncertain.

6.62 The ESC noted that weight-based disutility values remained uncertain. The ESC also considered that the model should have explored the impact of removing/altering the impact of gender with additional sensitivity analyses. Although there will likely be a higher proportion of females than males treated in clinical practice, 75% applied to

the model based on the STEP 1 trial may be an overestimate. This was revised in the PSCR base case, which included a single age and gender-neutral baseline utility value of 0.782, for subjects with BMI 18-24.9, as reported in Norman 2013. The ESC considered this did not account for the higher treatment effect in females which will underestimate the ICER if the proportion of treated patients that are female is lower than 75%. The ESC considered that sensitivity analyses using the revised baseline utilities and adjusting the female:male split would be informative. The PBAC agreed.

6.63 The pre-PBAC response provided a summary of population size and ICER estimates by various BMI/comorbidity categories, based on the PSCR-revised model. These estimates are shown in Table 17 below and have not been evaluated.

**Table 17: Estimated eligible populations (ABS 2017/18) and associated ICERs (cost/QALY)**

Persons ≥ 18 years		Excluding T2DM			
		Number of comorbidities			
BMI (kg/m <sup>2</sup> )		≥0	≥1	≥2	≥3
≥25	Population	11,483,700	6,346,500	2,553,700	626,300
	ICER (\$)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>2</sup>
≥30	Population	5,228,100	3,236,500	1,395,600	396,100
	ICER (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>5</sup>
≥35	Population	1,899,400	1,273,300	601,900	212,500
	ICER (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>1</sup>
≥40	Population	644,600	455,100	225,000	88,000
	ICER (\$)	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>4</sup>	█ <sup>4</sup>

Source: Table 1, p1, pre-PBAC response.

Note: ICERs calculated using the revised PSCR model. As presented in the PSCR, the revised base-case ICER for the BMI≥35 + ≥1 comorbidity population upon which funding is sought is \$75,000 to < \$95,000/QALY.

The redacted values correspond to the following ranges:

<sup>1</sup> \$95,000 to < \$115,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$55,000 to < \$75,000

<sup>4</sup> \$135,000 to < \$155,000

<sup>5</sup> \$155,000 to < \$255,000

### **Drug cost/patient/year**

6.64 The estimated drug cost of semaglutide was \$█ per patient per year, based on 13 scripts per year using the effective DPMQ \$█, and an assumption of perfect adherence.

**Table 18: Calculation of drug cost per year**

	STEP-1 target subgroup population	Economic model <sup>a</sup>	Financial estimates
Semaglutide script cost	-	\$ (effective DPMQ)	\$ (effective DPMQ)
Treatment adherence	NR	100% (13 scripts per year)	100% (13 scripts per year)
Treatment persistence	83.2% at 68 weeks	65.5% at 28 weeks; cumulative 49.0% at 52 weeks; With 5% annual discontinuations after 18 months	87.6% at 28 weeks; cumulative 71.2% at 52 weeks; With 5% annual discontinuations after 2 years

Source: STEP-1 subgroup analyses report; individual patient data from the STEP-1 trial included in the semaglutide economic model; Table 4-2 (p 196) of the submission

<sup>a</sup> Original uncorrected estimates of treatment persistence, corrected estimates using appropriate time points for continuation rules were 80.2% at 28 weeks and 57.1% at 52 weeks

6.65 The submission estimated lower treatment persistence in the economic model and budget impact analysis due to the application of the proposed continuation rules ( $\geq 5\%$  weight lost at 28 weeks,  $\geq 10\%$  weight loss at 52 weeks). The reasons for the difference in treatment persistence between the economic model and budget impact analyses were unknown.

### **Estimated PBS usage & financial implications**

6.66 The submission was considered by DUSC. The submission used an epidemiological approach to estimate utilisation and the financial impact of listing semaglutide 2.4 mg for patients with severe obesity who have at least one weight-related comorbidity but who do not have diabetes. Key inputs relied on in the financial estimates are summarised in Table 19 below.

**Table 19: Key inputs for financial estimates**

Data	Value	Source	Comment
<b>Eligible population</b>			
Australian adults with severe obesity (BMI $\geq 35$ kg/m <sup>2</sup> )	2,180,000 (in 2017)	ABS National Health Survey 2017-18, commissioned dataset	The long-term (chronic) health conditions in the ABS data did not match the weight-related comorbidities in the requested restriction.
% with $\geq 1$ weight-related comorbidity	71.3%		
% with $\geq 1$ weight-related comorbidity without diabetes	81.9%		
Annual growth of eligible population	2017-2023: 10.42% Annual growth 2024-2028: 1.53% to 1.36%	Based on the percentage growth in the projected Australian adult population from ABS population projections- 3222.0 Series B.	It is unclear whether overall population growth is an accurate indicator of growth in the eligible patient population. DUSC considered the growth likely underestimated. The National Health Survey data show that the proportion of Australian adults categorised as obese had increased from 27.9% to 31.3% from 2014-15 to 2017-18, suggesting that growth in the obese population is increasing beyond population growth.

Public Summary Document – March 2022 PBAC Meeting

Data	Value	Source	Comment
<b>Treatment utilisation</b>			
Uptake rate	17% in Year 1 decreasing to 15% in Year 6	Based on projections by the sponsor. The submission claimed that decreasing uptake rates were appropriate due to pent-up demand when semaglutide is launched, which will diminish over time.	The uptake rates are highly uncertain. No details were provided on the sources used to estimate these uptake rates. DUSC considered these rates likely underestimated as marketing for semaglutide for obesity will be significant and patient expectation will also be high.
Continuation past 28/52 weeks	87.6%/81.3%	Retrospective application of continuation rule ( $\geq 5\%$ weight loss at 28 weeks; $\geq 10\%$ weight loss at 52 weeks) to individual patient data for the target subgroup population in STEP-1	Treatment persistence estimates used in the budget impact analysis (28 weeks: 87.6%; cumulative estimate at 52 weeks: 71.2%) were inconsistent with those used in the economic model (28 weeks 80.2%; cumulative estimate at 52 weeks: 57.1%, corrected). The reasons for these differences were unknown. The budget impact analysis did not account for patients discontinuing therapy for adverse events or other reasons in the first two years of treatment
Continuation in subsequent years	95%	Assumption	No justification was provided for this assumption.
Adherence	100%	Assumption	100% adherence is unlikely to be realised in clinical practice.

Source: Table 4-2 (p 196) of the submission; Section 4 Excel workbook.

Abbreviations: ABS, Australian Bureau of Statistics; excl, excluding; pts, patients.

6.67 The estimated utilisation and financial implications (using the effective DPMQ) of a PBS listing for semaglutide 2.4 mg for severe obesity is summarised in Table 20 below. Errors were identified during the evaluation in the calculation of the number of eligible patients not already treated, and in the number of scripts for the initial year of treatment. Corrected estimates are shown below.

**Table 20: Estimated utilisation and financial impact of semaglutide 2.4 mg (effective DPMQ)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients meeting eligibility criteria	1	1	1	1	1	1
Patients already receiving semaglutide treatment <sup>a</sup>	2	3	13	15	17	21
Eligible patients (not already on semaglutide)	1	1	1	1	18	22
Uptake	17%	17%	16%	16%	15%	15%
Initiating patients	3	3	8	8	8	8
Continuing patients						
After 28 weeks (87.6%)	3	3	8	8	8	8
After 52 weeks (81.3%)	-	3	8	8	8	23
After 2nd year (95%)	-	-	8	8	8	8
After 3rd year (95%)	-	-	-	8	8	8
After 4th year (95%)	-	-	-	-	8	8
After 5th year (95%)	-	-	-	-	-	8
Initiation scripts to 28 weeks <sup>b</sup>	1	1	1	1	18	18
Continuation scripts <sup>b</sup>	1	9	10	14	16	19
<b>Total scripts</b>	4	10	14	16	19	24
Cost to PBS/RPBS (\$)	5	11	11	11	11	11
Co-payments (\$)	6	12	12	12	20	20
<b>Net cost to PBS/RPBS (\$)</b>	7	11	11	11	11	11

Source: Table 4-2 (p 196), Table 4-3 (p 197) of the submission.

Abbreviations: DPMQ, dispensed price for maximum quantity

<sup>a</sup> The submission calculated the number of patients already on semaglutide treatment (and ineligible to initiate treatment) based on the proportion of patients receiving any treatment in the previous year compared to the prevalent population in the previous year to derive a percentage which was then applied to the current year. This approach miscalculated the number of patients already on treatment and was corrected during the evaluation by simply using the reported number of continuing patients beyond 28 weeks in each year.

<sup>b</sup> There was an error in the calculation of scripts for the first year of treatment for each cohort of initiating patients. The submission's calculations inappropriately adjusted for patient-years of therapy which resulted in ~1.1 scripts per patient during the first 28 weeks. During the evaluation this was corrected to 7 scripts/patient.

The redacted values correspond to the following ranges:

- 1 1,000,000 to < 2,000,000
- 2 < 500
- 3 200,000 to < 300,000
- 4 2,000,000 to < 3,000,000
- 5 \$900 million to < \$1 billion
- 6 \$70 million to < \$80 million
- 7 \$800 million to < \$900 million
- 8 100,000 to < 200,000
- 9 3,000,000 to < 4,000,000
- 10 4,000,000 to < 5,000,000
- 11 > \$1 billion
- 12 \$100 million to < \$200 million
- 13 300,000 to < 400,000
- 14 6,000,000 to < 7,000,000
- 15 400,000 to < 500,000
- 16 7,000,000 to < 8,000,000
- 17 500,000 to < 600,000
- 18 900,000 to < 1,000,000
- 19 8,000,000 to < 9,000,000
- 20 \$200 million to < \$300 million

<sup>21</sup> 600,000 to < 700,000

<sup>22</sup> 800,000 to < 900,000

<sup>23</sup> 90,000 to < 100,000

<sup>24</sup> 9,000,000 to < 10,000,000

- 6.68 The net cost of listing semaglutide on the PBS/RPBS was estimated to be \$800 million to < \$900 million in year 1, increasing to > \$1 billion per year in the sixth year of listing, a cumulative total cost of > \$1 billion over 6 years (original uncorrected estimate > \$1 billion). The submission suggested this should be interpreted in the context of the size of the target population and the costs of managing obesity, estimated as \$11.8 billion in 2018 (The Obesity Collective, 2019). For further context, the DUSC noted that the total PBS expenditure in the 2020-21 financial year was \$13.8 billion.
- 6.69 Including patients with diabetes in the eligible patient population increased the cost to the PBS/RPBS from a base case of > \$1 billion to > \$1 billion over the first six years of listing; and including all patients with BMI  $\geq 35$  kg/m<sup>2</sup> increased the total net cost further to > \$1 billion over the first six years of listing.
- 6.70 There is substantial uncertainty with respect to the proportion of severely obese patients meeting the comorbidity criterion, the expected uptake rate of semaglutide and predicted treatment compliance in clinical practice. Overall, the DUSC considered that the financial impact may have been underestimated due to underestimation in the uptake rates and a large potential for use outside the restriction for overweight and obese people who have a BMI between 25 and 35 kg/m<sup>2</sup>. The continuation rules may also be difficult to enforce.
- 6.71 The DUSC also noted that:
- The intervention in the trial was a multi-component intervention, and there was a risk that as the first obesity treatment listed on the PBS, the medicine may become a dominant driver of the model of care unless a multi-component intervention is adequately funded. Despite the submission's statement that the budget impact of listing should be interpreted in the context of over \$11 billion annual costs due to obesity, the DUSC considered it is quite possible that the PBS costs will not be offset, due to the lack of funding for multi-component programs that would enable consumers to attain the outcomes reported in the trials.
  - There are no costs included for GP management plans / Team Care Arrangements, dietetics services and exercise physiology services.
  - There are no costs for managing adverse gastrointestinal events, yet patients in the trials required additional medication to manage these adverse events.
- 6.72 The DUSC and ESC had considered that there may be both episodic use and uncertain persistence due to the adverse event profile.

### **Quality Use of Medicines**

- 6.73 No quality use of medicines information was included in the submission.
- 6.74 The DUSC was concerned that the submission had given no consideration to the Category D pregnancy classification of the medicine and women of child-bearing age. The DUSC considered this issue was particularly relevant as women who are trying to get pregnant may be advised to lose weight to improve fertility and one third of pregnancies are unplanned. The pre-PBAC response considered that this was a regulatory issue.
- 6.75 The DUSC was also concerned that patients may take semaglutide but not realise health benefits if weight is regained after stopping treatment, or if concurrent dietary and exercise programs are not accessible.

### **Financial Management – Risk Sharing Arrangements**

- 6.76 The sponsor acknowledged that the magnitude of expected financial impact and uncertainty around the total impact means that a Risk Sharing Arrangement will be necessary. However, the submission stated that the form of the agreement had not yet been developed in detail.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommended the listing of semaglutide for the treatment of obesity. The PBAC recognised the high burden of disease in Australia and welcomed input from a stakeholder forum prior to the PBAC meeting. However, the submission had poorly justified the population access it had requested, the modelled benefits were highly uncertain, and the listing would not be cost-effective at the requested price. Furthermore, the PBAC considered that pharmacotherapy was only one aspect of the public health response to obesity in Australia, but the proposed semaglutide PBS listing would require an extremely high investment with very uncertain implications for the PBS and broader health budget.
- 7.2 The PBAC noted that there are currently no treatments for obesity available via the PBS, although several are TGA registered. The PBAC considered that that the consumer comments and the *National Obesity Strategy 2022-2032* demonstrated that equitable access to medicines for obesity treatment, as part of a holistic treatment approach, was important to the Australian community.
- 7.3 In terms of the clinical place in therapy for semaglutide, the PBAC:
- considered semaglutide should be used as a later-line treatment following previous attempts to lose weight with diet and exercise. It would be appropriate for the restriction to explicitly reflect this positioning, although the PBAC recognised that ‘previous attempts’ would be difficult to define uniformly in practice.

- agreed with the submission that semaglutide should be used as adjunct to diet and exercise, consistent with the intervention in the key clinical trials and the proposed TGA indication. The PBAC noted the ESC's advice that patients should be managed by a multidisciplinary care team, as well as the pre-PBAC response that this would create an access issue for patients. The PBAC recognised this issue but considered that semaglutide would need to be part of a multi-component intervention to treat obesity and align with public health interventions to address the burden of obesity more broadly.
- advised that excluding patients with type 2 diabetes from initiating semaglutide 2.4 mg raised equity issues and was not well justified by the submission, given that patients with pre-diabetes would be eligible to initiate and patients who develop diabetes would be eligible to continue treatment. The PBAC also noted and agreed with the ESC advice that the submission did not address the value of weight loss in each of the subpopulations and it is unclear whether weight loss in diabetic patients has a smaller, similar or greater impact on downstream complications compared to non-diabetic patients.
- noted the submission proposed targeting treatment by BMI and comorbidity status, and that treatment was intended as a chronic therapy to maintain weight loss over time and reduce the downstream complications of obesity. However, the PBAC considered this did not reflect the cyclical nature of weight loss and weight gain, and there was a high risk of intermittent use due to the adverse event profile of semaglutide, and patients discontinuing therapy when weight loss goals achieved, then restarting once weight is regained. Patients receiving multiple treatment cycles rather than continuous treatment contributes to the uncertainty of the modelled benefits (see further below). In view of this, the PBAC considered that the submission preference for availability of semaglutide for chronic use was not supported by the clinical trials and one option could be to limit the lifetime treatment duration available via the PBS to better align with the available evidence from the STEP trials.
- considered there may be a more defined role for semaglutide to achieve short-term weight loss prior to bariatric and other surgery, to improve surgical outcomes, as was discussed at the stakeholder meeting.
- noted the DUSC's advice semaglutide is a Category D drug that should not be used in patients attempting pregnancy. The PBAC noted that further emphasis on this issue was expected in the final Product Information and considered that a resubmission should justify the intended population with the pregnancy classification in mind.

7.4 The PBAC noted that revisions to the requested PBS restriction would be needed to reflect any revised place in therapy. Furthermore, the PBAC considered that:

- A streamlined authority level was unlikely to be appropriate due to the potential for use outside the restriction.
  - A request for nurse practitioner prescribing for continuation would require further justification as none had been provided.
  - To better provide for dose flexibility, the restriction could be structured with an initial titration phase, initial maintenance phase, first continuing phase and subsequent continuing phase (as proposed by the Secretariat).
  - The continuation rules proposed did not adequately account for cyclical use of semaglutide and the circumstances under which patients might stop and then re-start therapy (including restricting non-responders from continued access).
  - The BMI criteria should be adjusted for, at a minimum, Asian and Aboriginal and/or Torres Strait Islander populations.
- 7.5 The PBAC considered that the proposed comparator (placebo in conjunction with diet and exercise) was reasonable, given there are no subsidised drugs for obesity on the PBS and the limited access bariatric surgery in Australia. However, PBAC also noted the data referenced by DUSC on the effectiveness of phentermine–topiramate (see ‘Comparator’ heading) and the current and proposed MBS funding for bariatric surgeries, and considered the requested substantial cost of listing semaglutide had not been considered within this context.
- 7.6 The PBAC noted that the submission was based on five head-to-head randomised double-blind trials and an off-treatment extension study (STEP-1 to 5, and STEP-1 extension), with a co-primary outcome of mean change in body weight over time and the proportion of patients achieving > 5% weight loss from baseline. The PBAC agreed with the ESC observations in paragraph 6.39 regarding the limitations with the trial data in that there was: no long-term data demonstrating a reduction in downstream complications of obesity; there was limited long-term safety data; and uncertain applicability in terms of patient populations and circumstances of use, including the level of diet and exercise counselling available in the Australian setting. In addition, the *post hoc* analyses presented had some limitations as outlined in paragraphs 6.25 and 6.26. The PBAC noted that large ongoing cardiovascular outcomes trial (SELECT, n=17,500) is due for completion in September 2023, and considered that the results of this trial would provide additional clarity about the extent of cardiovascular benefit for this potentially widely used new therapy.
- 7.7 Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable for weight loss, HbA1c and other biomarkers, and quality of life over the trial duration and whilst on treatment, although it was unlikely that these benefits would be fully realised in Australian practice without the intensive diet and exercise counselling co-administered in the trial program. These benefits would also likely be diminished if semaglutide were used intermittently. Moreover, despite the favourable effects on the short-term and surrogate outcomes the clinical effectiveness on clinical

endpoints remained uncertain.

- 7.8 The PBAC agreed with the submission's claim that semaglutide with diet and exercise had inferior comparative safety compared to placebo with diet and exercise. Notably, the PBAC also agreed with the ESC that these adverse events would contribute to intermittent use of semaglutide outside of a trial setting.
- 7.9 The PBAC noted the ESC's advice that the base case cost-effectiveness estimate (\$15,000 to < \$25,000 per QALY gained) should not be considered reliable due to specific issues with the key drivers of the model noted in paragraph 6.57, and additional issues raised during the evaluation in paragraph 6.51. Although the PSCR had presented a revised base case, with a number of corrections and revised inputs shown in paragraph 6.61, the weight-based disutilities remained uncertain, the submission had not explored different female:male population distributions, and the modelled long-term reductions in health outcomes remained highly uncertain and likely optimistic. Moreover, at \$75,000 to < \$95,000 per QALY gained, the ICER was unacceptably high. The PBAC also noted that the pre-PBAC response had presented the PSCR-revised model with varying BMI/comorbidity criteria, shown in Table 17, but the PBAC considered that any revisions to these criteria alone would not address the uncertainty associated with the long-term outcomes.
- 7.10 In terms of the financial impact, the PBAC noted that the submission had proposed average annual expenditure on semaglutide in the order of █% of the annual PBS budget. The PBAC also noted the DUSC's advice that the estimates were uncertain and likely underestimated, and had not incorporated costs of multidisciplinary care, diet/exercise services, or adverse events. Even with a Risk Sharing Arrangement, expenditure of > \$1 billion over 6 years represented a substantial opportunity cost for the PBS and health budgets. Although the submission had suggested this be interpreted in the context of substantial expenditure on the costs of managing obesity, it was not clear that any offsets would be realised and indeed there was potential, as noted by the DUSC, that there would be inadequate funding available for other aspects of obesity treatment, which may mean that the proposed benefits of semaglutide are not realised in practice, given that semaglutide – and indeed pharmacotherapy generally – is only one component of the public health response to obesity.
- 7.11 The PBAC considered a resubmission for semaglutide should address the following issues:
- Additional justification for the proposed population and who are most likely to benefit and in whom semaglutide is cost effective.
  - The uncertainty of modelled reductions in obesity-related comorbidities. The PBAC also advised that without clinical trial evidence of long-term benefits, a resubmission should be based on valuing the outcomes of shorter-term weight loss as seen under the conditions of the STEP trials.
  - The potential for intermittent use of semaglutide and the impact on downstream

benefits claimed. This should be addressed across the restriction, clinical data, economic model and financial estimates.

- Revised financial estimates in accordance with any revised population and circumstances of use.

The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

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

**Outcome:**

Not recommended

## **8 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.

## **9 Sponsor's Comment**

The sponsor had no comment.