

7.06 SEMAGLUTIDE,

Injection 0.25 mg in 0.5 mL pre-filled single dose pen

Injection 0.5 mg in 0.5 mL pre-filled single dose pen

Injection 1.0 mg in 0.5 mL pre-filled single dose pen

Injection 1.7 mg in 0.75 mL pre-filled single dose pen

Injection 2.4 mg in 0.75 mL pre-filled single dose pen,
Wegovy[®],

NOVO NORDISK PHARMACEUTICALS PTY. LIMITED

1 Purpose of submission

1.1 The standard re-entry resubmission requested a General Schedule Authority Required (Telephone/Online) listing for the treatment of severe obesity despite prior participation in an appropriate lifestyle-based weight management intervention.

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 resubmission

Component	Description
Population	Adult patients with BMI \geq 35 kg/m² <u>40 kg/m²</u> and at least one <u>two</u> weight-related comorbidity <u>comorbidities</u> who have a confirmed diagnosis of at least one of: obstructive sleep apnoea, knee osteoarthritis or pre-diabetes; but who do not have diabetes. <u>Patients must have participated in an appropriate lifestyle-based weight management intervention in the previous 12 months.</u>
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 an individually tailored and clinically appropriate weight management program.
Comparator	Placebo. To be used in conjunction with an individually tailored and clinically appropriate weight management program.
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 is superior in terms of effectiveness and inferior in terms of safety compared to placebo.

Source: Table 1-4, p20 of the resubmission

Note: Key changes compared to the March 2022 submission are marked using underline and ~~strike through~~

*The downstream complications of obesity were not explicitly valued in the current resubmission

1.3 The resubmission acknowledged PBAC's previous concerns about the lack of long-term data to support a reduction in obesity complications with semaglutide treatment (para 7.6 and 7.7, semaglutide Public Summary Document [PSD], March 2022 PBAC meeting). The resubmission also noted PBAC advice that, given the limitations of the data, it may be more appropriate to focus on the shorter-term benefits of weight loss (para 7.11, semaglutide PSD, March 2022 PBAC meeting). Consequently, the resubmission focused on the clinical evidence for weight loss and the associated impacts on quality of life. The PBAC recalled that, in March 2022, it had also noted that a large ongoing cardiovascular outcomes trial (SELECT, n=17,500) was due for

completion in September 2023, and that the results of this trial would provide additional clarity about the extent of cardiovascular benefit for this potentially widely used new therapy (para 7.6, semaglutide PSD, March 2022 PBAC meeting).

2 Background

Registration status

- 2.1 Semaglutide (single-dose pen, Wegovy®) was approved by the TGA on 1 September 2022 as an ‘adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial BMI of ≥ 30 kg/m² (obesity), or ≥ 27 kg/m² to < 30 kg/m² (overweight) in the presence of at least one weight-related comorbidity’.
- 2.2 Although TGA-approved, at the time of the November 2023 PBAC meeting, Wegovy® was not available in Australia and the sponsor had not advised TGA when the product will be launched.
- 2.3 A new TGA application for semaglutide single-dose pens was initiated in January 2023, to extend the indication ‘as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with obesity or overweight and at least one weight-related comorbidity’. Obesity (BMI ≥ 95 th percentile) and overweight (BMI ≥ 85 th percentile) are as defined on sex- and age-specific BMI growth charts (CDC.gov).
- 2.4 Semaglutide (multi-dose pen, Ozempic®) is also 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’.

Previous PBAC consideration

- 2.5 The sponsor presented a Category 2 submission to the March 2022 PBAC meeting requesting a General Schedule Authority Required (Streamlined) PBS listing for semaglutide single-dose pens for the treatment of severe obesity. The submission proposed a PBS restriction allowing semaglutide to be used as a chronic therapy in adult patients with BMI ≥ 35 kg/m² and at least one (from a list of 20 pre-specified) weight-related comorbidity but who do not have diabetes. The clinical data were based on the STEP clinical trial program (predominantly the STEP-1 trial). The economic analysis was based on a complex cost-effectiveness/cost utility analysis that included both short-term and long-term treatment benefits associated with weight loss. The budget impact analysis was based on an epidemiological approach informed by multiple data sources and assumptions.
- 2.6 The PBAC did not recommend the listing on the basis that the proposed target population was poorly justified, 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 (para 7.1, semaglutide PSD, March 2022 PBAC meeting).

2.7 Table 2 presents a high-level summary of PBAC’s advice for a resubmission, and how the resubmission addressed these concerns.

Table 2: PBAC advice for a resubmission

Matter of concern (March 2022 PBAC meeting)	Addressed in the resubmission
Advice for a resubmission	
<p>The PBAC considered a resubmission for semaglutide should address the following issues (para 7.11):</p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • The narrower proposed population was informed by exploratory subgroup analyses of transformed SF-6Dv1 data from the STEP trials and advice from clinical experts. • The economic model has been revised, based on quality of life improvements from weight loss over the short-term. • The resubmission proposed that patients who discontinue therapy must have a minimum treatment gap of 2 years before they are allowed to re-initiate therapy. The resubmission acknowledged there are no clinical data on semaglutide re-treatment. The impact of re-treatment was included in the financial estimates, but not the economic model. • The financial estimates were revised, based on the narrower proposed population, allowing for treatment re-initiation after 2 years, and incorporating costs to the MBS associated with multidisciplinary care.

Source: Table 1-1, pp14-15 of the resubmission; Semaglutide PSD, March 2022 PBAC meeting
 Abbreviations: PBAC, Pharmaceutical Benefits Advisory Committee; SF-6Dv1, Short Form 6 dimension version 1

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	AEMP (\$)	DPMQ (\$)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SEMAGLUTIDE						
INITIAL TREATMENT – DOSE TITRATION						
Semaglutide, pre-filled single dose pen, 0.25 mg in 0.5 mL	█ (published) (effective)	█ (published) (effective)	1	4	0	Wegovy
Semaglutide, pre-filled single dose pen, 0.5 mg in 0.5 mL	█ (published) (effective)	█ (published) (effective)	1	4	0	
Semaglutide, pre-filled single dose pen, 1.0 mg in 0.5 mL	█ (published) (effective)	█ (published) (effective)	1	4	0	
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.75 mL	█ (published) (effective)	█ (published) (effective)	1	4	0	

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INITIAL TREATMENT – DOSE MAINTENANCE						
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	2	Wegovy
Semaglutide, pre-filled single dose pen, 2.4 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	2	
FIRST CONTINUING TREATMENT						
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	3	Wegovy
Semaglutide, pre-filled single dose pen, 2.4 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	3	
SECOND CONTINUING TREATMENT						
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	5	Wegovy
Semaglutide, pre-filled single dose pen, 2.4 mg in 0.75 mL	(published) (effective)	(published) (effective)	1	4	5	
Category / Program: General Schedule						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)						
PBS Indication: Class III obesity						
Treatment Phase: Initial treatment – dose titration						
Clinical criteria:						
Patient must have a Body Mass Index greater than or equal to 40 kg/m ² [or 37 kg/m ² for patients with Asian or Aboriginal or Torres Strait Islander ethnicity];						
AND						
Clinical criteria:						
Patient must have a confirmed diagnosis of at least two weight related comorbidities;						
AND						
Clinical criteria:						
Patient must have a confirmed diagnosis of either obstructive sleep apnoea, osteoarthritis of the knee, or prediabetes;						
AND						
Clinical criteria:						
Patient must not have diabetes mellitus;						
AND						
Clinical criteria:						
Patient must have participated in an appropriate lifestyle-based weight management intervention within the previous 12 months;						
AND						
Clinical criteria:						
Patient must not have discontinued PBS-subsidised treatment with this drug for this condition within the previous two years;						
AND						
Clinical criteria:						
Patient must not receive more than 16 weeks of treatment under this restriction						
Treatment criteria:						
The treatment must be adjunct to receiving clinically appropriate dietetic and weight management advice						
Population criteria:						
Patient must be aged 18 years or older						
Prescribing Instructions:						

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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 two of the following weight related comorbidities must be recorded in the patient's medical record: 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
A confirmed diagnosis of at least one of the following specific weight related comorbidities must be recorded in the patient's medical record: obstructive sleep apnoea, osteoarthritis of the knee, or prediabetes
Participation in an appropriate lifestyle-based weight management intervention within the last 12 months must be documented in the patient's medical record
Discontinuation of previous treatment with this drug is defined as any period of 3 or more months where no prescription was filled
Treatment Phase: Initial treatment – dose maintenance
Clinical criteria:
Patient must have completed the initial PBS-subsidised 16-week dose titration with this drug for this condition;
AND
Clinical criteria:
The treatment must not exceed 12 weeks of dose maintenance under this restriction
Treatment criteria:
The treatment must be adjunct to receiving clinically appropriate dietetic and weight management advice
Population criteria:
Patient must be aged 18 years or older
Treatment Phase: First continuing treatment
Clinical criteria:
Patient must have completed the initial – dose maintenance PBS-subsidised treatment with this drug for this condition;
AND
Clinical criteria:
The treatment must not exceed 16 weeks of dose maintenance under this restriction
Treatment criteria:
The treatment must be adjunct to receiving clinically appropriate dietetic and weight management advice
Population criteria:
Patient must be aged 18 years or older
Treatment Phase: Subsequent continuing treatment
Clinical criteria:
Patient must have completed the first continuing PBS-subsidised treatment with this drug for this condition at their most recent treatment course; OR
Patient must have previously received PBS-subsidised treatment with this drug for this condition under this restriction;
AND
Clinical criteria:
Patient must have achieved and maintained a reduction of at least 10% from the initial baseline body weight while being treated with this drug for this condition
Treatment criteria:
The treatment must be adjunct to receiving clinically appropriate dietetic and weight management advice
Population criteria:
Patient must be aged 18 years or older

3.1 During the evaluation, it was noted that the resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account

for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods, as presented in this document.

- 3.2 The resubmission proposed tiered effective prices for semaglutide dose strengths:
- A published DPMQ of \$| per script for semaglutide 0.25 mg, 0.5 mg and 1.0 mg dose strengths and an effective DPMQ of \$| per script (|% rebate).
 - A published DPMQ of \$| per script for semaglutide 1.7 mg dose strength and an effective DPMQ of \$| per script (|% rebate).
 - A published DPMQ of \$| per script for semaglutide 2.4 mg dose strength and an effective DPMQ of \$| per script (|% rebate).
- 3.3 In contrast, the March 2022 submission proposed flat pricing for semaglutide with a published DPMQ of \$| and an effective DPMQ of \$| (|% rebate).
- 3.4 Semaglutide for type 2 diabetes is currently subject to a special pricing arrangement with a published DPMQ of \$133.80 and an effective DPMQ of \$| (|% rebate) for both the 1.5 mL and 3.0 mL multi-dose pens (used to deliver 0.25, 0.5 and 1.0 mg doses).
- 3.5 The proposed PBS restriction (BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities including a confirmed diagnosis of at least one of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes) is narrower than the approved TGA indication and clinical trial populations (BMI ≥ 30 kg/m², or ≥ 27 kg/m² with at least one comorbidity) and is narrower than the previously requested PBS restriction in the March 2022 submission (BMI ≥ 35 kg/m² with at least one comorbidity). The resubmission stated that the targeting of treatment to such a defined subgroup was responsive to previous PBAC advice, and was explicitly economic, financial and practical in nature; as the sponsor strongly believes that from a clinical perspective, the appropriate place for semaglutide in the management of overweight and obesity is defined by its much broader TGA indication.
- 3.6 The evaluation noted it was unclear whether the target population represents the best use of semaglutide on the PBS compared to other alternatives such as using semaglutide as a short-term weight loss treatment prior to bariatric surgery, as suggested by both stakeholders and the PBAC (para 7.3, semaglutide PSD, March 2022 PBAC meeting). The ESC advised that, while there was no direct evidence to support the use of semaglutide as a bridge to bariatric surgery, its use in this role would be reasonable. Additionally, the resubmission did not address the implementation of the proposed criteria in clinical practice as it is likely that there will be use outside of the restriction in patients who may benefit from treatment but who do not meet the restriction requirements.
- 3.7 The ESC considered that the trial-based list of comorbidities in the proposed restriction failed to narrow the restriction sufficiently, and advised that the list should potentially be reduced to a small number of comorbidities representing higher risk

and disease burden, with additional definitions included in the restriction. The ESC noted that a higher risk group might include patients with at least two of: coronary artery disease, cerebrovascular disease, peripheral artery disease, obstructive sleep apnoea, pre-diabetes (impaired fasting glucose or impaired glucose tolerance) without diabetes mellitus, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and osteoarthritis of the hip or knee.

- 3.8 The ESC discussed whether the list of comorbidities should also recognise the effects of severe obesity on mental health and whether it would be appropriate to include mental health problems as well as physical health problems in the restriction list. The ESC recognised the difficulty in defining this but considered that depression or anxiety requiring pharmacological or cognitive behavioural therapy might be appropriate comorbidity descriptors.
- 3.9 The ESC also proposed that an alternative approach to the restriction could be to use a validated scoring system, for example the Edmonton Obesity Staging System, in conjunction with BMI with or without age.
- 3.10 The ESC noted that the Aboriginal and Torres Strait Islander population was included with a lower BMI threshold of 37 kg/m² (37.5 kg/m² is considered equivalent to a BMI of 40 kg/m² (obesity class III) in the general population, according to Australian Obesity Classification System and Management Algorithm¹). This inclusion was in response to the PBAC's previous consideration that the BMI criteria should be adjusted for, at a minimum, Asian and Aboriginal and/or Torres Strait Islander populations (para 7.4, semaglutide PSD, March 2022 PBAC meeting). Alternatively, recognising that Aboriginal and Torres Strait Islander populations were a higher risk population for chronic health conditions, the ESC proposed that identifying as an Aboriginal and/or Torres Strait Islander person could be one of the qualifying comorbidities.
- 3.11 The ESC considered that a telephone/online authority was appropriate given the high risk of use outside the restriction, but also recognised that that this would have significant flow-on consequences for Services Australia.
- 3.12 The resubmission acknowledged PBAC concerns regarding the proposed place in therapy (para 7.3, semaglutide PSD, March 2022 PBAC meeting), with the proposed restriction now including a criterion requiring patients to have participated in an appropriate lifestyle-based weight management intervention within the previous 12 months. The proposed restriction also stated that semaglutide should be used as an adjunct to clinically appropriate dietetic and weight management advice. However, the resubmission stated that the sponsor does not believe the PBS restriction can or should seek to more specifically define what might constitute 'appropriate' precursor or concomitant interventions, or how these might be provided in practice. The

¹ <https://www.diabetessociety.com.au/documents/ObesityManagementAlgorithm18.10.2016FINAL.pdf>

resubmission stated that appropriateness will be intrinsically individual, based on multiple patient-specific factors and circumstances, that could not be captured in a PBS General Schedule restriction. However, the resubmission stated that the sponsor will defer to the PBAC regarding the appropriate definition, composition, provision and funding of the precursor and concomitant lifestyle-based weight management interventions.

- 3.13 The clinical evidence supporting the use of semaglutide is based on its use as part of a multi-component intervention alongside diet and exercise, with regular lifestyle counselling every 4 weeks by a dietitian or similar healthcare professional. DUSC had previously raised concerns regarding the limited access to subsidised adjunctive weight management care in Australia. DUSC had stated that it would be prudent to consider how the system could support funding, and effective large-scale implementation, of a multi-component program that enables true consumer participation for these hard to treat conditions. DUSC had noted from the experience of subsidising medicines for pain and many mental health conditions, where structural reforms are needed for multi-modal care, that the medicine can often become the dominant driver of the model of care, potentially with unsatisfactory outcomes for patients, as the full benefits of a multimodal management program are not realised due to reliance on unidimensional interventions (semaglutide DUSC advice, March 2022 PBAC meeting). DUSC had also previously noted that adjunct weight management care should be referred to as a program (which carries an expectation of ongoing treatment) rather than advice. In addition, the PBAC had previously noted that the 'National Obesity Strategy 2022-2032' encompasses a range of interventions, not just pharmacotherapy, and that any resubmission would need to be considered in this context (para 3.11, semaglutide PSD, March 2022 PBAC meeting).
- 3.14 The PBAC previously stated that the sponsor's 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 (para 7.3, semaglutide PSD, March 2022 PBAC meeting). The resubmission stated that semaglutide is intended for the chronic management of obesity and therefore did not agree with or propose a maximum duration of therapy. The Pre-Sub-Committee Response (PSCR) claimed that limiting the lifetime treatment duration available via the PBS is not clinically optimal or cost effective. The resubmission proposed a continuation rule restricting treatment to patients who achieve a 10% weight reduction by 68 weeks (consistent with the timeframe of the STEP-1 trial). The resubmission did not adequately justify the responder threshold proposed in the restriction, given that a reduction in body weight of at least 5% over 1 year is widely accepted as a clinically important change (and was used as a primary outcome in the clinical trials), while a reduction in body weight of more than 15% is the recommended treatment goal for patients in the target population based on current Australian guidelines (Markovic 2022). The PSCR commented that the 10% threshold was consistent with discussion at the Semaglutide

Stakeholder Meeting (Outcome Statement, August 2021), and many publications (Cefalu et al. 2015). The resubmission did not adequately address how this criterion could be implemented without a significant risk of use in patients who may receive some benefit but who may not have met this treatment target.

- 3.15 The ESC considered that assessment of response should be made between 12 and 68 weeks after commencement of therapy. The maximum quantities provided under the first 3 phases only provide up to 44 weeks of treatment and this will need to be amended to accommodate up to 68 weeks of treatment to achieve 10% weight loss.
- 3.16 The resubmission acknowledged PBAC concerns regarding intermittent or cyclical use of semaglutide (para 7.4, semaglutide PSD, March 2022 PBAC meeting) and proposed that patients who discontinue therapy must have a minimum treatment gap of 2 years before they are allowed to re-initiate therapy. The resubmission acknowledged there are no clinical data on semaglutide re-treatment. Despite the lack of data, it may be appropriate to allow patients to re-initiate therapy, as their circumstances may change over time. However, the optimal duration of any exclusion period is unclear. The PSCR reiterated that the 2-year period had been ‘pragmatically selected’ and was intended to motivate treatment adherence and persistence and prevent intermittent or cyclical use in the PBS setting. The ESC considered that prevention of re-initiation for a 2-year period or any lengthy exclusion period would be highly likely to reduce the short- and long-term clinical benefits of semaglutide. It may also drive inappropriate behaviours, as patients may continue to claim scripts in order to retain the ability to use semaglutide in future. The ESC also acknowledged that the removal of this requirement would have significant financial impacts at the requested price.
- 3.17 The resubmission proposed that any medical practitioner should be allowed to prescribe semaglutide. The resubmission argued that this was reasonable given that: the target population remains relatively large and will initially present in a primary care setting; publicly funded specialist obesity services in Australia are limited; and obesity is significantly more prevalent in lower socioeconomic groups for whom healthcare access and affordability is already critical and challenging. For patients in the target population, the current Australian guidelines recommend that care should be provided by a specialist-led multidisciplinary team (Markovic 2022). The ESC considered it would be impractical to restrict prescribing to specialist prescribers.
- 3.18 The resubmission advised it is likely that semaglutide 2.4 mg will be launched in the private market some months prior to PBS-listing and it was requested that appropriate grandfathering arrangements are made for those patients who are eligible to continue treatment. However, the resubmission did not provide any details on grandfathering and stated that this would require further consideration and input from the PBAC Secretariat. The ESC considered that any grandfathering arrangements for this population would raise significant financial, logistic and equity of access issues. The ESC advised that if grandfathering were provided, it should only be for patients who had met the initial PBS restriction at the time of their treatment initiation.

- 3.19 Additional issues with the restriction to be addressed included the maximum quantities in the initial 3 treatment phases not allowing sufficient duration of treatment before the stopping rule could be assessed, and the assumption that MBS Team Care Arrangements would be available to provide a similar level of adjunctive care as seen in the trials.

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

4 Population and disease

- 4.1 Obesity is a complex chronic disease 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, and the lack of structural features of the built environment that promote an active lifestyle (Sansbury and Hill 2014).
- 4.2 Obesity is a highly prevalent disease in the Australian population which has been steadily increasing over time, with the latest estimate indicating that approximately 1 in 3 adults are obese (ABS National Health Survey 2017-2018).
- 4.3 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.
- 4.4 The resubmission claimed that there is a clinical need for semaglutide given that few people living with obesity manage to achieve and maintain weight loss through lifestyle modification alone. The resubmission claimed that the 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.
- 4.5 The resubmission stated that, from a clinical perspective, the most appropriate place for semaglutide is for the broader overweight/obese population consistent with the clinical trial population and approved TGA indication (BMI ≥ 30 kg/m², or BMI ≥ 27 kg/m² with at least one comorbidity). However, the resubmission acknowledged the need to target the PBS population to a smaller subset of patients who may be more likely to achieve quality of life improvements from weight loss over the short-term in order to assure the cost-effectiveness was more robust and reduce the logistical and financial impact of listing semaglutide on the PBS.

- 4.6 Based on *post hoc* analyses of SF-6Dv1 utility data from the STEP-1 and STEP-2 trials, the resubmission selected a preferred population of patients with BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities including a confirmed diagnosis of at least one of: obstructive sleep apnoea, knee osteoarthritis or pre-diabetes; but who do not have diabetes.
- 4.7 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.
- 4.8 The resubmission positioned semaglutide as a second-line treatment option after previous lifestyle interventions (diet and exercise). Treatment with semaglutide should be used alongside lifestyle modification, incorporating elements of a reduced calorie diet and increased physical activity. Semaglutide is intended to be used as a chronic therapy in order to maintain weight improvements over time.
- 4.9 The resubmission acknowledged that semaglutide is a Pregnancy Category D medicine (drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage) but made no further statement. DUSC had previously raised concerns about the use of semaglutide in women of child-bearing age given that women who are trying to get pregnant may be advised to lose weight to improve fertility and one third of pregnancies are unplanned. The previous PSCR considered that this was a regulatory issue (para 6.74, semaglutide PSD, March 2022 PBAC meeting).
- 4.10 Semaglutide has been subject to ongoing worldwide supply issues due to increased demand for its use as a weight management therapy. At the time of the November 2022 PBAC meeting, the TGA noted there is limited supply of semaglutide in Australia and it has been actively working with the sponsor, wholesalers and healthcare professionals to manage the ongoing shortage². The resubmission did not address when the sponsor will be able to provide semaglutide in sufficient quantities to supply both the type 2 diabetes and the overweight/obesity indications. At the time of the PBAC meeting, the sponsor had not advised TGA when Wegovy[®] will be launched in Australia.

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

² <https://www.tga.gov.au/safety/shortages/information-about-major-medicine-shortages/about-ozempic-semaglutide-shortage-2022-and-2023>

5 Comparator

- 5.1 The resubmission nominated placebo (as a proxy for no pharmacological therapy) in conjunction with diet and exercise as the main comparator. The main argument in support of this nomination was that the PBAC previously accepted this comparator in the March 2022 submission, given that there are no subsidised drugs for obesity on the PBS and the limited access to bariatric surgery in Australia (para 7.5, semaglutide PSD, March 2022 PBAC meeting).
- 5.2 The previous consideration by PBAC was in the context of a broader requested patient population (patients with BMI ≥ 35 kg/m² and at least one weight-related comorbidity) and the same consideration may not apply to the narrower patient population requested in the resubmission (patients with BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with a confirmed diagnosis of at least one of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes).
- 5.3 In particular, it is unclear whether bariatric surgery should be considered a secondary comparator in the narrower target population. The PBAC previously noted that approximately 50,000 patients received MBS-listed bariatric services annually between 2013-2017 (para 5.4, semaglutide PSD, March 2022 PBAC meeting) which is likely to substantially overlap with the population expected to be treated with semaglutide under the proposed restriction (estimated to be approximately 100,000-200,000 patients per year). The PSCR reiterated that access to bariatric surgery in Australia is very limited and highly unlikely to be the therapy most replaced in practice. The ESC considered that, while this argument from the PSCR in relation to bariatric surgery as a comparator was not unreasonable, it also noted that bariatric surgery has been shown to be cost-effective in a number of studies and comparative cost-effectiveness had not been established.
- 5.4 During the evaluation it was noted that both oral semaglutide and tirzepatide are potential near market comparators for this indication. The ESC noted that tirzepatide was not recommended by PBAC for diabetes mellitus and that no submission had been made to the PBAC for weight loss. It also noted that the sponsor asserted [redacted] plans for a PBS submission for oral semaglutide. At the time of the PBAC meeting, the TGA had accepted an application for tirzepatide as 'an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management'.³

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

³ <https://www.tga.gov.au/resources/prescription-medicines-under-evaluation/mounjaro-eli-lilly-australia-pty-ltd>

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 (104), health care professionals (32) and organisations (10) via the Consumer Comments facility on the PBS website. Comments were strongly supportive of making semaglutide available on the PBS for the treatment of obesity. Individuals and healthcare professionals discussed: the impact of obesity on physical and mental health, and quality of life; the stigma and prejudice associated with the disease; the health benefits associated with weight loss; the potential impact of treatment in particular population groups (e.g. young people and women with infertility); the importance of a multi-disciplinary approach to obesity treatment; the need for adequate training for healthcare professionals; and the known/manageable side effects of semaglutide treatment.

6.3 The PBAC also appreciated the input received from the following organisations:

- Australian College of Nurse Practitioners
- Australia and New Zealand Obesity Society
- The Alfred
- Impact Obesity
- National Aboriginal Community Controlled Health Organisation
- National Paediatric Medicines Forum
- Health Consumers' Council (WA)
- Liver Foundation
- Arthritis Australia
- Weight Issues Network

6.4 These organisations made comments on a range of themes including: equity concerns as obesity disproportionately affects people with limited financial means; the particular health needs of certain populations affected by obesity (Aboriginal and Torres Strait Islander people, women, adolescents, and those living with non-alcoholic fatty liver disease); the negative impacts and costs of obesity on individuals and the health system as a whole; the clinical evidence supporting the health benefits of semaglutide treatment; support for comprehensive diet and nutrition programs to accompany pharmacotherapy (including public funding of such programs); the need for healthcare professional training; and the ongoing urgency for preventative health programs for obesity.

Clinical trials

6.5 The resubmission included data from five head-to-head randomised trials comparing semaglutide to placebo in the STEP clinical trial program (STEP 1-5). The resubmission also presented new *post hoc* subgroup analyses of the STEP-1 trial.

6.6 Details of the included studies are provided in the Table 3.

Table 3: Studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
NN9536-4373 (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
	IQVIA (2022). Health economics and outcomes research statistical report: Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity.	Internal study report
	Wilding, <i>et al</i> (2021). Once-weekly semaglutide in adults with overweight or obesity.	New England Journal of Medicine 384: 989-1002
NN9536-4374 (STEP-2)	Kushner et al (2021a). Once-weekly subcutaneous semaglutide 2.4 mg reduces body weight in adults with overweight or obesity regardless of baseline characteristics (STEP 1).	Journal of the Endocrine Society A24 [abstract & poster only]
	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
NN9536-4375 (STEP-3)	Davies, <i>et al</i> (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.	Lancet 397: 971-984
	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
NN9536-4376 (STEP-4)	Wadden, <i>et al</i> (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.	Journal of the American Medical Association 325: 1403-1413
	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
NN9536-4378 (STEP-5)	Rubino, <i>et al</i> (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.	Journal of the American Medical Association 325: 1414-1425
	Novo Nordisk (2021). Two-year effect and safety of semaglutide 2.4 mg once weekly in subjects with overweight or obesity.	Internal study report
	Garvey, <i>et al</i> (2022). Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial.	Nature Medicine 28: 2083-2091

Source: Table 2-4, p45 of the resubmission

6.7 The resubmission noted a recently completed cardiovascular outcomes trial of semaglutide compared to placebo in overweight/obese patients with established cardiovascular disease (SELECT; actual completion June 2023). The resubmission also

noted recently completed or ongoing studies in populations with obesity and knee osteoarthritis (STEP-9; estimated completion September 2023), pre-diabetes (STEP-10; actual completion January 2023) or preserved-ejection fraction heart failure (STEP-HFpEF; actual completion April 2023). However, these trials were excluded from the resubmission as no results were available.

6.8 During the preparation of the commentary, top-line results from the SELECT trial were released by the sponsor via press release, which indicated that semaglutide treatment was associated with a 20% relative risk reduction in major cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) compared to placebo in overweight/obese patients with established cardiovascular disease. However, at the time of the PBAC meeting, this trial had not been published in a peer-reviewed journal.

6.9 Full trial results from the STEP-HFpEF trial were also published in September 2023 (Kosiborod 2023). These results were not evaluated in full but indicated that treatment with semaglutide was associated with statistically significant improvements in the Kansas City Cardiomyopathy Questionnaire clinical summary score compared to placebo in overweight/obese patients with preserved ejection fraction heart failure.

6.10 The key features of the included studies are summarised in Table 4.

Table 4: 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	Overweight/obese patients without diabetes	Weight, biomarkers, quality of life and adverse events	Individual patient data from <i>post hoc</i> subgroups
STEP-2	1,210	MC, R, DB, AC/PC, (Semaglutide 1.0 mg active control) 75 weeks duration	Low	Overweight/obese Patients with diabetes	Weight, biomarkers, quality of life and adverse events	Not used
STEP-3	611	MC, R, DB, PC, 75 weeks duration	Low	Overweight/obese patients 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	Overweight/obese patients without diabetes	Weight, biomarkers, quality of life and adverse events	Not used
STEP-5	304	MC, R, DB, PC, 104 weeks duration	Low	Overweight/obese patients without diabetes	Weight, biomarkers and adverse events	Not used

Source: Section 2.3, pp47-56; Section 2.4, pp57-77 of the resubmission

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

Comparative effectiveness

- 6.11 Treatment with semaglutide was associated with a statistically significant reduction in body weight over time, with a treatment difference of 10-12% compared to placebo in non-diabetic patients with and without adjunctive intensive behavioural therapy (STEP-1, STEP-3, STEP-5).
- 6.12 Treatment with semaglutide 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).
- 6.13 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.
- 6.14 A larger proportion of patients achieved each weight loss threshold ($\geq 5\%$, $\geq 10\%$, $\geq 15\%$, $\geq 20\%$) with semaglutide compared to placebo in the STEP trials. The differences between treatment arms were statistically significant in all trials.
- 6.15 A larger proportion of patients achieved each weight loss threshold with semaglutide 2.4 mg compared to semaglutide 1.0 mg in patients with diabetes, although the differences between arms were substantially smaller than observed for the placebo comparison.
- 6.16 Treatment with semaglutide 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).
- 6.17 Other quality of life outcomes also favoured semaglutide compared to placebo although the differences were generally small between treatment arms and variable between trials.
- 6.18 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 (STEP-2).
- 6.19 Treatment with semaglutide was also associated with improvements in glucose metabolism, blood pressure and lipid metabolism compared to placebo.
- 6.20 No pre-specified subgroup analyses were identified in any of the included trial reports for the STEP clinical trial program.

- 6.21 The resubmission presented extensive *post hoc* subgroup analyses of the STEP-1 trial based on various combinations of baseline BMI, number of comorbidities and presence/absence of specific comorbidities (obstructive sleep apnoea, knee osteoarthritis, pre-diabetes). There were substantial imbalances in the proportion of females and the proportion with pre-diabetes between treatment arms for many of the subgroups. Additionally, there were notable imbalances in the proportions of patients with obstructive sleep apnoea and knee osteoarthritis between treatment arms in some of the smaller subgroup populations. Overall, the comparison of baseline characteristics suggests that the results of the subgroup analyses, particularly for smaller subgroups, should be interpreted with caution.
- 6.22 The resubmission did not present any of the results of *post hoc* subgroup analyses and treatment interaction testing that were previously identified during the March 2022 evaluation process (Kushner 2021). These analyses indicated that a slightly greater response to semaglutide was seen in female patients, white as opposed to other racial groups, patients starting the trial with a lower baseline body weight and in patients without diabetes or prediabetes. The largest differences were associated with gender (estimated treatment difference in mean body weight for females: 16.3%, males: 9.4%; interaction testing $p < 0.001$) 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%; interaction testing $p < 0.001$) (para 6.25, semaglutide PSD, March 2022 PBAC meeting).
- 6.23 Key *post hoc* subgroup analyses of the mean change in body weight with semaglutide and placebo in the STEP-1 trial are summarised in Table 5.

Table 5: Key subgroup analyses of mean percentage change in body weight from baseline in the STEP-1 trial

Subgroup	Semaglutide Mean %	Placebo Mean %	Treatment difference Mean % (95% CI)
ITT (N=1,961)	-14.85	-2.41	-12.44 (-13.37, -11.51)
BMI ≥ 35 kg/m ² and ≥ 2 weight-related comorbidities with OSA or KOA (N=273; 13.9% of trial population)	-13.64	-1.81	-11.83 (-13.96, -9.70)
BMI ≥ 40 kg/m ² and ≥ 1 weight-related comorbidity with OSA or KOA (N=167; 8.5% of trial population)	-12.84	-2.01	-10.83 (-13.43, -8.23)
BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with OSA or KOA (N=142; 7.2% of trial population)	-12.84	-2.23	-10.61 (-13.47, -7.76)
BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with OSA, KOA or PD (N=257; 13.1% of trial population)	-13.01	-2.16	-10.85 (-13.19, -8.51)

Source: Table 2-70, p144 of the resubmission; Table 166, p338; Table 167, p339; Table 172, p341; Table 173, p342; Table 174, p342 of the STEP-1 subgroup analysis report

Abbreviations: BMI, body mass index; CI, confidence interval; KOA, knee osteoarthritis; OSA, obstructive sleep apnoea; PD, pre-diabetes

Note: Green shading indicates the main target population in the resubmission

- 6.24 Treatment with semaglutide was associated with a statistically significant reduction in body weight compared to placebo in the intention to treat (ITT) population and across all nominated subgroups. However, the magnitude of difference between treatments was generally smaller in the subgroup populations compared to the ITT population.
- 6.25 Key *post hoc* subgroup analyses of the proportions of patients achieving a 5% or 10% reduction in body weight with semaglutide and placebo in the STEP-1 trial are

summarised in Table 6. The resubmission did not provide estimates of the proportion of patients achieving a 15% reduction in body weight, which is the guideline recommended target for patients with a BMI ≥ 40 kg/m² with weight-related comorbidities (Markovic 2022).

Table 6: Key subgroup analyses of the proportion of patients with weight loss in the STEP-1 trial

Subgroup	$\geq 5\%$ reduction from baseline			$\geq 10\%$ reduction from baseline		
	SEMA Odds	PBO Odds	Odds ratio (95% CI)	SEMA Odds	PBO Odds	Odds ratio (95% CI)
ITT (N=1,961)	5.03	0.45	11.22 (8.88, 14.19)	1.95	0.13	14.68 (11.08, 19.44)
BMI ≥ 35 kg/m ² and ≥ 2 weight-related comorbidities with OSA or KOA (N=273; 13.9% of trial population)	6.49	0.35	18.68 (9.55, 36.51)	1.43	0.14	9.87 (4.90, 19.91)
BMI ≥ 40 kg/m ² and ≥ 1 weight-related comorbidity with OSA or KOA (N=167; 8.5% of trial population)	5.90	0.33	18.03 (7.65, 42.50)	1.38	0.14	9.99 (4.11, 24.29)
BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with OSA or KOA (N=142; 7.2% of trial population)	5.56	0.30	18.24 (7.22, 46.11)	1.33	0.17	7.99 (3.21, 19.89)
BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with OSA, KOA or PD (N=257; 13.1% of trial population)	4.66	0.36	13.03 (6.83, 24.88)	1.38	0.14	9.68 (4.75, 19.73)

Source: Table 2-71, p145 of the resubmission; Table 184, p347; Table 185, p 348; Table 190, p350; Table 191, p351; Table 192, p351; Table 202, p356; Table 203, p357; Table 208, p359; Table 209, p360; Table 210, p360 of the STEP-1 subgroup analysis report
Abbreviations: BMI, body mass index; CI, confidence interval; KOA, knee osteoarthritis; OSA, obstructive sleep apnoea; PBO, placebo; PD, pre-diabetes; SEMA, semaglutide

Note: Green shading indicates the main target population in the resubmission

- 6.26 Treatment with semaglutide was associated with statistically significantly higher proportions of patients achieving a 5% or 10% reduction in body weight compared to placebo in the ITT population and across all nominated subgroups.
- 6.27 Key *post hoc* subgroup analyses of SF-36 scores (physical component and mental component summary scores) with semaglutide and placebo in the STEP-1 trial are summarised in Table 7.

Table 7: Key subgroup analyses of mean change in SF-36 scores in the STEP-1 trial

Subgroup	Semaglutide, Mean (SD)			Placebo, Mean (SD)			Treatment difference (95% CI)
	Baseline	Week 68	Change	Baseline	Week 68	Change	
ITT (N=1,961)							
SF-36 PCS ^a	51.1 (7.3)	53.6 (7.3)	2.4 (6.7)	51.1 (7.9)	51.4 (8.7)	0.2 (7.1)	1.96 (1.31, 2.61)
SF-36 MCS ^b	55.4 (5.7)	54.0 (7.2)	-1.5 (7.1)	55.5 (5.9)	53.4 (7.9)	-2.1 (7.7)	0.92 (0.10, 1.73)
BMI ≥35 kg/m² and ≥2 weight-related comorbidities with OSA or KOA (N=273; 13.9% of trial population)							
SF-36 PCS ^a	46.5 (8.0)	49.6 (8.6)	2.9 (7.6)	45.7 (8.4)	45.0 (9.8)	-0.5 (7.6)	3.30 (1.43, 5.16)
SF-36 MCS ^b	56.8 (5.4)	54.9 (7.2)	-1.7 (5.9)	57.1 (5.6)	54.2 (8.6)	-2.1 (6.4)	0.93 (-1.02, 2.88)
BMI ≥40 kg/m² and ≥1 weight-related comorbidity with OSA or KOA (N=167; 8.5% of trial population)							
SF-36 PCS ^a	44.7 (8.2)	49.2 (8.6)	4.4 (8.2)	43.7 (8.7)	43.3 (10.5)	0.1 (8.0)	4.28 (1.80, 6.75)
SF-36 MCS ^b	56.2 (6.2)	54.1 (8.0)	-2.1 (7.3)	57.0 (6.4)	54.3 (9.1)	-2.5 (7.9)	0.55 (-2.13, 3.23)
BMI ≥40 kg/m² and ≥2 weight-related comorbidities with OSA or KOA (N=142; 7.2% of trial population)							
SF-36 PCS ^a	44.7 (8.2)	49.0 (9.0)	4.2 (8.4)	43.2 (8.4)	42.1 (10.5)	-0.4 (8.3)	4.60 (1.80, 7.41)
SF-36 MCS ^b	56.0 (6.3)	53.8 (8.5)	-2.1 (7.7)	57.0 (6.6)	53.8 (9.8)	-2.9 (8.3)	0.67 (-2.38, 3.71)
BMI ≥40 kg/m² and ≥2 weight-related comorbidities with OSA, KOA or PD (N=257; 13.1% of trial population)							
SF-36 PCS ^a	46.5 (8.7)	50.5 (8.5)	4.3 (8.0)	45.8 (8.8)	45.9 (10.9)	0.7 (7.7)	3.22 (1.25, 5.19)
SF-36 MCS ^b	56.5 (5.6)	54.1 (8.0)	-2.4 (7.4)	57.6 (5.4)	54.4 (8.7)	-2.9 (7.5)	0.44 (-1.80, 2.67)

Source: Section 11.5.1, pp112-117 of the STEP-1 trial report; additional data from information request provided by the Sponsor
Abbreviations: BMI, body mass index; CI, confidence interval; KOA, knee osteoarthritis; MCS, mental component summary; OSA, obstructive sleep apnoea; PCS, physical component summary; PD, pre-diabetes; SD, standard deviation

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

^b SF-36 Mental component summary scores range from -3.83 to 78.75; higher scores indicate better quality of life

Note: Green shading indicates the main target population in the resubmission

- 6.28 Overall, patients with higher baseline BMI and/or higher comorbidity burden appeared to have worse physical component scores, but similar mental component scores compared to the ITT population. Treatment with semaglutide was associated with modest improvements in physical component scores (2-4 point increase on a 74 point scale) compared to placebo across all nominated subgroups. There were minimal differences in mental component scores between treatment arms.
- 6.29 The ESC also discussed an analysis of the Household, Income and Labour Dynamics in Australia (HILDA) survey, which explored interactions between level of obesity, multiple comorbidities and quality of life.⁴ It was noted that a plot (Figure 3 of the publication) of the mean values of the SF-36 composite measures and the health utility index (SF-6D) by BMI category indicated a qualitative difference (lower quality of life) for patients with morbid obesity (BMI ≥ 40 kg/m²). The ESC considered that this analysis generally supported the relevance of improved quality of life outcomes for the proposed target PBS population.
- 6.30 Treatment with semaglutide was also associated with a substantial increase in the proportion of patients with normoglycaemia over time compared to placebo across all nominated subgroups. Further analyses indicated that the treatment effect of

⁴ Keramat SA, Alam K, Keating B, et al. Morbid obesity, multiple long-term conditions, and health-related quality of life among Australian adults: Estimates from three waves of a longitudinal household survey. *Prev Med Rep.* 2022; 28:101823. Published 12 May 2022. <https://doi.org/10.1016/j.pmedr.2022.101823>

semaglutide on glycaemic status is at least partially independent of weight changes (Table 221, pp490-507 of the STEP-1 subgroup analysis report).

Comparative harms

- 6.31 Treatment with semaglutide 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 trials. Adverse events were more frequent during the initial titration phase but continued to occur throughout the treatment period.
- 6.32 Frequent adverse events ($\geq 5\%$ of subjects) that occurred more often in the semaglutide 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 ($\geq 2\%$ but $< 5\%$) that occurred more often in the semaglutide 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 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. prokinetics), diarrhoea (e.g. anti-prokinetics), 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. However, the pattern of adverse events was similar for both dose strengths (predominantly gastrointestinal and nervous system disorders).
- 6.35 Key *post hoc* subgroup analyses of safety outcomes with semaglutide and placebo in the STEP-1 trial are summarised in Table 8.

Table 8: Key subgroup analysis of the adverse events from the STEP-1 trial

Subgroup	Semaglutide (%)		Placebo (%)	
	Incidence, patients (%)	Frequency, events per 100 patient years	Incidence, patients (%)	Frequency, events per 100 patient years
ITT (N=1,961)				
Any adverse event	1171 (89.7%)	566	566 (86.4%)	398
Probably-related adverse event	571 (43.7%)	126	147 (22.4%)	40
Possibly-related adverse event	726 (55.6%)	158	223 (34.0%)	67
Serious adverse event	128 (9.8%)	10	42 (6.4%)	6
Adverse event leading to discontinuation	92 (7.0%)	7	20 (3.1%)	3
BMI \geq35 kg/m² and \geq2 weight-related comorbidities with OSA or KOA (N=273; 13.9% of trial population)				
Any adverse event	170 (93.9%)	642	89 (96.7%)	592
Probably-related adverse event	84 (46.4%)	131	27 (29.3%)	43
Possibly-related adverse event	109 (60.2%)	178	34 (37.0%)	80
Serious adverse event	23 (12.7%)	13	8 (8.7%)	10
Adverse event leading to discontinuation	11 (6.1%)	6	1 (1.1%)	1
BMI \geq40 kg/m² and \geq1 weight-related comorbidity with OSA or KOA (N=167; 8.5% of trial population)				
Any adverse event	102 (94.4%)	724	56 (94.9%)	546
Probably-related adverse event	56 (51.9%)	156	19 (32.2%)	45
Possibly-related adverse event	72 (66.7%)	197	17 (28.8%)	62
Serious adverse event	14 (13.0%)	15	5 (8.5%)	9
Adverse event leading to discontinuation	7 (6.5%)	6	1 (1.7%)	1
BMI \geq40 kg/m² and \geq2 weight-related comorbidities with OSA or KOA (N=142; 7.2% of trial population)				
Any adverse event	87 (94.6%)	722	47 (94.0%)	598
Probably-related adverse event	47 (51.1%)	154	18 (36.0%)	52
Possibly-related adverse event	62 (67.4%)	207	17 (34.0%)	73
Serious adverse event	13 (14.1%)	16	5 (10.0%)	11
Adverse event leading to discontinuation	6 (6.5%)	6	1 (2.0%)	2
BMI \geq40 kg/m² and \geq2 weight-related comorbidities with OSA, KOA or PD (N=257; 13.1% of trial population)				
Any adverse event	149 (89.2%)	645	84 (93.3%)	531
Probably-related adverse event	76 (45.5%)	140	27 (30.0%)	44
Possibly-related adverse event	94 (56.3%)	173	35 (38.9%)	79
Serious adverse event	24 (14.4%)	14	9 (10.0%)	13
Adverse event leading to discontinuation	9 (5.4%)	5	3 (3.3%)	3

Source: Table 2-75, p149 of the resubmission; Table 225, p509; Table 226, p510; Table 231, p513; Table 232, p514; Table 233, p515 of the STEP-1 subgroup analysis report

Abbreviations: BMI, body mass index; ITT, intention to treat; KOA, knee osteoarthritis; OSA, obstructive sleep apnoea; PD, pre-diabetes

Note: Green shading indicates the main target population in the resubmission

- 6.36 Overall, the risk of adverse events in both treatment arms appeared to increase in subgroups with higher baseline BMI and comorbidities compared to the ITT population. Treatment with semaglutide 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 across all nominated subgroups.
- 6.37 During the evaluation, the sponsor provided updated data on potential safety concerns with semaglutide based on a Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report (June 2021 to May 2022). The report included use of injectable (single dose and multi dose pens) and oral semaglutide, predominantly for type 2 diabetes and weight management.

- 6.38 No new safety concerns were identified. Important identified risks include gastrointestinal adverse events (specifically nausea, vomiting and diarrhoea), acute gallstone disease (cholelithiasis), severe hypoglycaemia in combination with oral anti-diabetic treatments and/or insulin, diabetic retinopathy complications and acute pancreatitis. Important potential risks include serious allergic reactions, neoplasms (malignant and non-malignant), medullary thyroid cancer and pancreatic cancer. The Periodic Benefit Risk Evaluation Report identified missing information in regard to pregnancy and lactation as well as patients with severe hepatic impairment.
- 6.39 The report acknowledged a high reporting rate of medication errors with semaglutide single-dose pens used for weight management. The report stated that these errors were predominantly related to administration errors (insufficient pressure applied and premature retraction of the device from the skin by the patient) and prescribing/dispensing errors (starting dose too high). The report noted that higher starting doses may increase the risk of gastrointestinal events with semaglutide but otherwise concluded that the safety implications of these medication errors were limited.
- 6.40 At the time of evaluation and ESC consideration, the European Medicines Agency was investigating safety signals regarding suicidal ideation and self-injurious ideation, as well as thyroid cancer with GLP-1 analogues including semaglutide (EMA Pharmacovigilance Risk Assessment Committee [PRAC], 8 May 2023; 31 July 2023). At the time of the PBAC meeting, the EMA had concluded that the available evidence does not support a causal association between GLP-1 analogues and thyroid cancer (EMA PRAC Meeting highlights, 27 October 2023).
- 6.41 Overall, there remain limited long-term data to support the safety of the new higher dose of semaglutide for obesity.

Benefits/harms

- 6.42 A summary of the comparative benefits and harms for semaglutide versus placebo for the requested population is presented in Table 9.

Table 9: Summary of comparative benefits and harms for semaglutide and placebo in patients with BMI \geq 40 kg/m² and \geq 2 weight-related comorbidities with a confirmed diagnosis of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes

Subgroup	Semaglutide	Placebo	Treatment difference
Proportion of patients with \geq 10% reduction in body weight from baseline to Week 68	57.98%	12.28%	45.7%
Proportion of patients with normoglycaemia at Week 68	74.9%	43.3%	31.6%
Mean change in SF-36 PCS score from baseline to Week 68	4.3	0.7	3.22
Serious adverse event rate requiring hospitalisation over 68 Weeks	14.4%	10.0%	4.4%

Source: Table 2-71, p145; Table 2-74, p148; Table 2-75, p149 of the resubmission; additional data from information request provided by the Sponsor

Abbreviations: PCS, physical component summary

Note: SF-36 Physical component summary scores range from 6.11 to 79.67; higher scores indicate better quality of life

6.43 Based on the target subgroup in the STEP-1 trial (BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with a confirmed diagnosis of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes), for every 100 patients treated with semaglutide in comparison with placebo over 68 weeks, there would be:

- 46 additional patients who would achieve $\geq 10\%$ weight loss.
- A modest improvement in the physical components of quality of life (average improvement of 3 points on a 74-point scale).
- 32 additional patients with normoglycaemia.
- 5 additional serious adverse event requiring hospitalisation.

6.44 A summary of the comparative benefits and harms for semaglutide versus placebo for the overall trial population is presented in Table 10.

Table 10: Summary of comparative benefits and harms for semaglutide and placebo in the ITT population of the STEP-1 trial

ITT	Semaglutide	Placebo	Treatment difference
Proportion of patients with $\geq 10\%$ reduction in body weight from baseline to Week 68	66.1%	11.5%	54.6%
Proportion of patients with normoglycaemia at Week 68	84.6%	63.1%	21.5%
Mean change in SF-36 PCS score from baseline to Week 68	2.4	0.2	2.2
Serious adverse event rate requiring hospitalisation over 68 Weeks	9.8%	6.4%	3.4%

Source: Table 2-71, p145; Table 2-74, p148; Table 2-75, p149 of the resubmission; additional data from information request provided by the Sponsor

Abbreviations: ITT, intention to treat; PCS, physical component summary

Note: SF-36 Physical component summary scores range from 6.11 to 79.67; higher scores indicate better quality of life

6.45 Based on the target subgroup in the STEP-1 trial (BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with a confirmed diagnosis of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes), for every 100 patients treated with semaglutide in comparison with placebo over 68 weeks, there would be:

- 55 additional patients who would achieve $\geq 10\%$ weight loss.
- A modest improvement in the physical components of quality of life (average improvement of 2 points on a 74-point scale).
- 22 additional patients with normoglycaemia.
- 4 additional serious adverse event requiring hospitalisation.

Clinical claim

6.46 The resubmission described semaglutide as superior in terms of effectiveness (quality of life, weight loss and related parameters, glucose metabolism) and inferior in terms of safety compared to placebo. The ESC considered that this claim was reasonable, but that the magnitude of benefit in practice remained uncertain.

6.47 The ESC also noted that the following issues should be considered:

- The real-world effectiveness of semaglutide in clinical practice compared to the reported efficacy in clinical trial settings given the potential for differences in circumstances of use (e.g. suboptimal compliance to semaglutide and/or adjunctive weight management). The PSCR considered that as adjunctive weight management was also used in the placebo arms in the core STEP program, ‘it is only the synergistic effects of the composite intervention which might be overestimated in the trials compared to the real world.’
 - The robustness of the subgroup analyses, as the subgroup populations were identified *post hoc*, patient allocation to treatment arms was not stratified based on the nominated variables, and many of the analyses were based on small patient numbers with notable and potentially important imbalances in patient characteristics between treatment arms at baseline. The PSCR commented that the main imbalance was a slightly higher proportion of females in the placebo arm than treatment arm (86.7% vs 72.5%), which was unlikely to favour the treatment arm since female sex was generally associated a slightly greater response to semaglutide (para 6.22).
 - Limited long-term data to support the safety of higher maintenance doses of semaglutide (1.7 mg, 2.4 mg) used for obesity. The PSCR considered this issue was mitigated by over six years of use in a relatively large diabetes population.
- 6.48 The PBAC reaffirmed its previously held view 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.’ The PBAC also reaffirmed its view that ‘the inferior comparative safety claim was reasonable.’ (Paragraphs 6.41 and 6.42, semaglutide PSD, March 2022 PBAC meeting).
- 6.49 The PBAC also recalled its previous comment that, ‘despite the favourable effects on the short-term and surrogate outcomes the clinical effectiveness on clinical endpoints remained uncertain’. With regards to this issue, the PBAC noted that presentation of the SELECT trial results would have been informative.

Economic analysis

- 6.50 The sponsor developed a new economic analysis for the current resubmission instead of revising the economic analysis presented in the March 2022 submission, given the substantial issues raised regarding the previous economic model.
- 6.51 The resubmission presented a modelled economic evaluation of semaglutide compared to placebo for the treatment of severe obesity. The economic evaluation was based on a subgroup analysis of the STEP-1 trial with additional modelled data. The economic evaluation was presented as a cost-utility analysis.

6.52 The economic analysis was based on the initial episode of care only and did not account for subsequent episodes of treatment with semaglutide. The resubmission claimed that this approach was reasonable as there are insufficient clinical data available for semaglutide re-treatment. This approach was not adequately justified given that the proposed PBS restriction allows semaglutide re-treatment (after a treatment gap of at least 2 years). Additionally, the budget impact estimates include semaglutide re-treatment based on the assumption of no difference in treatment effects between the initial and re-treatment episodes of care.

6.53 Key components of the economic evaluation are summarised in Table 11.

Table 11: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years
Time horizon	5 years
Methods used to generate results	Markov cohort analysis
Treatments	Semaglutide (titrated to a dose of 2.4 mg weekly) or placebo in combination with a weight management program.
Model structure	Two health states during the first 68 weeks of the model (alive, dead) and three health states for the remainder of the model (alive with weight loss response, alive without weight loss response, dead). The model also tracked treatment status (on-treatment, off-treatment), glycaemic status (normoglycaemia, pre-diabetes) and serious adverse events to estimate costs over time.
Cycle length	28 days (no half-cycle correction)
Patient characteristics and circumstances of use	The resubmission modelled age, gender and glycaemic category based on reported baseline values from the combined treatment arms of the STEP-1 subgroup population with baseline BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with a confirmed diagnosis of at least one of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. The modelled circumstances of use included variable treatment persistence over time (see below) but assumed that all patients would titrate to the maximum dose and would be fully adherent with therapy. The model assumed that patients would only receive one episode of care with semaglutide, with no re-treatment. In regard to adjunctive weight management, it was assumed that all modelled patients would be managed through a team care arrangement which would be reviewed at regular intervals. Patients were assumed to receive dietician or exercise physiologist visits every 4 weeks for the first 68 weeks (consistent with the STEP-1 trial protocol) before switching to less intensive counselling for the remainder of model. The model assumed treatment persistence to pharmacological therapy and adjunctive weight management would be the same.
Transition probabilities	Patient survival was estimated based on general population mortality rates derived from Australian life tables in 2018-2022. Treatment response was estimated based on a <i>post hoc</i> analysis of the proportion of patients achieving a 10% reduction in bodyweight from baseline to Week 68 in the STEP-1 subgroup population with baseline BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with confirmed obstructive sleep apnoea, knee osteoarthritis or pre-diabetes (target population). Treatment status during the first 68 weeks of the model was based on a <i>post hoc</i> analysis of the proportion of patients prematurely stopping therapy in the STEP-1 target population (18.0% in the semaglutide arm and 24.4% in the placebo arm). At Week 68, modelled patients were assessed for response status; responders were assumed to remain on therapy, while non-responders discontinued therapy. A low risk of discontinuation beyond 68 weeks in treatment responders of 5% per year was assumed given these patients had already persisted with treatment for 68 weeks and achieved clinically relevant weight loss.

Component	Description
	<p>Glycaemic status during the first 68 weeks of the model was based on a <i>post hoc</i> analysis of the proportion of patients in each glycaemic category (normoglycaemia, pre-diabetes) in the STEP-1 target population. Glycaemic status between Week 68 and Week 104 was extrapolated based on the assumption that the distribution across glycaemic categories at Week 68 would be maintained over this period regardless of whether patients were persistent or non-persistent to therapy. Glycaemic status beyond Week 104 was extrapolated based on a <i>post hoc</i> analysis of glycaemic status in weight loss responders and non-responders using combined data from both treatment arms.</p> <p>Serious adverse events during the first 68 weeks were estimated based on a <i>post hoc</i> analysis of event rates in the STEP-1 target population (1.1% per cycle in the semaglutide arm and 1.0% per cycle in the placebo arm). It was assumed that no further serious adverse events occurred beyond 68 weeks.</p>
Utility values	<p>Utility values were estimated based on SF-36v2 data from a <i>post hoc</i> analysis of the STEP-1 subgroup population with baseline BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with confirmed obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. SF36v2 scores were transformed to SF-6Dv1 health states using a mapping tool developed by the University of Sheffield (no relevant reference provided) and using Australian utility weights (Norman 2014).</p> <p>Values between Week 68 and Week 104 were extrapolated based on the assumption that utility values at Week 68 would be maintained over this period regardless of whether patients were persistent or non-persistent to therapy.</p> <p>Utility values beyond Week 104 were extrapolated based on a <i>post hoc</i> analysis of Week 68 utility values in weight loss responders and non-responders using combined data from both treatment arms of the STEP-1 target subgroup.</p>
Costs	<p>Drug costs were estimated based on the proposed effective price of semaglutide. It was assumed that administration of semaglutide would also require additional GP visits for dose titration with costs based on the MBS fee.</p> <p>The costs associated with adjunctive weight management (i.e. team care arrangements, GP visits and allied health visits) were based on MBS fees.</p> <p>The cost of serious adverse events (\$2,226 per event) was based on AR-DRG cost weights.</p> <p>The cost of pre-diabetes (\$41.78 per cycle) was based on a costing study using data from the 2004-2005 Australian Diabetes, Obesity and Lifestyle study (Lee 2013).</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1-1, pp225-226 of the resubmission

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; BMI, body mass index; GP, general practitioner; MBS, Medicare Benefits Schedule.

- 6.54 The economic model was based on 3 distinct phases (trial period, first extrapolation period, second extrapolation period).
- 6.55 Patients begin the model in the trial period (first 16 cycles, up to Week 68) with baseline characteristics (age, gender, glycaemic status) based on the STEP-1 subgroup population with baseline BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with a confirmed diagnosis of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. During this period patients could remain alive or die due to general mortality. During this period, the model also captures changes in treatment status and glycaemic status, the incidence of serious adverse events and treatment arm utility values based on *post hoc* analyses of the target subgroup population.
- 6.56 Patients begin the first extrapolation period (cycles 17-26, up to the end of Year 2) based on their classification as a weight loss responder ($\geq 10\%$ weight loss) or

non-responder (< 10% weight loss) at Week 68. During this period, treatment responders could remain on therapy, discontinue therapy (and become non-responders), or die due to general mortality. All non-responders were assumed to discontinue therapy and could remain alive or die due to general mortality. During this period, the model assumed that glycaemic status and treatment utility values observed at Week 68 would be maintained to Week 104 regardless of treatment status. The ESC considered this approach was poorly justified and highly uncertain, unreasonably favouring semaglutide. The model also assumed that patients no longer experience serious adverse events during this period.

6.57 During the second extrapolation phase (cycles 27-65, Years 3-5), treatment responders could remain on therapy, discontinue therapy at a rate of 5% per year (and become non-responders), or die due to general mortality. Non-responders could remain alive or die due to general mortality. During this period, changes in glycaemic status and utility values were based on responder status rather than treatment arm estimates (which were used to inform the first 2 phases). The model assumed that patients no longer experience serious adverse events during this period.

6.58 Patients who discontinue therapy in the economic model were not allowed to re-initiate therapy. Therefore, the model does not provide an estimate of the cost-effectiveness associated with multiple cycles of treatment. The ESC considered this not reflective of likely clinical practice.

6.59 The estimated treatment and responder utility values are summarised in Table 12.

Table 12: Utility values used in the economic model

Variable	Semaglutide	Placebo	Source
Baseline	0.6506		STEP-1 trial. Based on SF-6Dv1 baseline values from the combined treatment arms for the subgroup population with baseline BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with obstructive sleep apnoea, knee osteoarthritis or pre-diabetes
Change from baseline to Week 8	-0.0055	-0.0741	STEP-1 trial. Based on SF-6Dv1 scores for each individual treatment arm from the subgroup population with baseline BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with obstructive sleep apnoea, knee osteoarthritis or pre-diabetes.
Change from baseline to Week 16	+0.0124	-0.0229	
Change from baseline to Week 20	+0.0231	-0.0436	
Change from baseline to Week 36	+0.0253	-0.0501	
Change from baseline to Week 52	+0.0550	-0.0379	
Change from baseline to Week 68	+0.0447	-0.0412	
Responder endpoint value at Week 68	0.7575		STEP-1 trial. Based on SF-6Dv1 values from the combined treatment arms for the subgroup population with baseline BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. Only the endpoint values were used in the model, which resulted in a change from modelled baseline of +0.1069 for responders and -0.0634 for non-responders.
Non-responder endpoint value at Week 68	0.5872		
Responder change from baseline to Week 68	+0.0784		
Non-responder change from baseline to Week 68	-0.0229		

Source: Table 2-78, p155; Table 3-2, p176 of the resubmission
Abbreviations: BMI, body mass index

- 6.60 The ESC noted a decline in quality of life was observed over one year for the placebo arm. It was considered this may reflect patients potentially being disheartened by not losing weight in the clinical trial. The ESC considered it was unlikely patients would have that much decline in quality of life outside a clinical trial setting if they are staying in the same health state/status quo. The pre-PBAC response disagreed with the ESC arguing that if an obese person was to participate in a lifestyle intervention of the intensity and duration required by the STEP trials and not achieve significant weight loss, it is entirely credible that they would experience an important decline in HRQoL/utility. The ESC also considered the fluctuation in utility values over the first year was unexplained, and noted that they were drawn from small sample. In all, the ESC considered the utility values utilised in the model to be highly uncertain.
- 6.61 In regard to adjunctive weight management, the resubmission assumed that all modelled patients would be managed through a team care arrangement, which would be reviewed at regular intervals (3 visits in the first 68 weeks then 1 visit every 24 weeks). The resubmission assumed patients would receive dietician or exercise physiologist visits every 4 weeks for the first 68 weeks (consistent with the STEP-1 trial) before switching to less intensive counselling, with 2 dietician or exercise physiologist visits every 24 weeks for the remainder of model. The model assumed treatment persistence to pharmacological therapy and adjunctive weight management would be the same. The ESC noted that this would unlikely be achieved in clinical practice due to shortages and wait lists already for these therapies.
- 6.62 The intensity and frequency of adjunctive weight management in the STEP-1 trial is unlikely to be representative of clinical practice. Reduced compliance to adjunctive weight management in clinical practice would generally be expected to lead to worse outcomes compared to the clinical trial setting. It is also unclear whether the treatment effects observed in STEP-1 trial can be maintained with less intensive counselling over the longer term. The ESC noted that these were not tested in the model, and thus the benefit modelled remains highly uncertain.
- 6.63 During the evaluation, a major calculation error was identified in which the utility value of responders was applied to non-responders in the semaglutide arm (correcting this error increased the incremental cost-effectiveness ratio from \$15,000 to < \$25,000 in the base case to \$25,000 to < \$35,000 per QALY gained).
- 6.64 Key drivers of the economic model are summarised in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Treatment arm utility values	<p>Utility values were estimated based on SF-36v2 data from a <i>post hoc</i> analysis of the STEP-1 subgroup population with baseline BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with confirmed obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. SF-36v2 scores were transformed to SF-6Dv1 health states using a mapping tool developed by the University of Sheffield (no relevant reference provided) and using Australian utility weights (Norman 2014).</p> <p>The transformed utility data did not appear to be consistent with the quality of life outcomes reported in the STEP-1 trial, which generally suggested much smaller differences between treatment arms.</p> <p>The resubmission did not adequately justify the mapping of SF-36v2 quality of life values to SF-6Dv1 health states given that SF-6Dv2 health states have been developed based on the SF-36v2 questionnaire (Brazier 2002, Mulhern 2020) which also has Australian valuation of health states (Mulhern 2021).</p> <p>A sponsor-commissioned, <i>post hoc</i> analysis of the STEP trials which transformed SF-36v2 scores to SF-6Dv2 utility values using UK QALY weights was recently published (Bjorner 2023). The estimated utility difference between semaglutide and placebo in the STEP-1 trial using mapped SF-6Dv2 values (0.029) was substantially smaller than the estimates presented in the resubmission using mapped SF-6Dv1 values (0.057). The pre-PBAC response stated the new methodological development was not actively considered during preparation of the resubmission and it also strongly disputes the assertion that an observed difference in the utility benefit obtained in the ITT population of STEP 1 using the UK valuation algorithm for the SF-6Dv2, versus the Australian valuation algorithm for the SF-6Dv1, means that the new methodology and value set will necessarily produce less favourable results than the old one within the subgroups of interest.</p> <p>Values between Week 68 and Week 104 were extrapolated based on the assumption that utility values at Week 68 would be maintained over this period regardless of whether patients were persistent or non-persistent to therapy. The ESC considered that this assumption was not appropriate given that approximately 42% of patients in the semaglutide arm and 88% of patients in the placebo arm had ceased therapy at Week 68 in the model.</p>	High, favours semaglutide
Responder status utility values	<p>Utility values beyond Week 104 were extrapolated based on a <i>post hoc</i> analysis of Week 68 mapped utility values (see above) in weight loss responders and non-responders using combined data from both treatment arms of the STEP-1 target subgroup.</p> <p>There were substantial differences in baseline utility scores between weight loss responders and non-responders, particularly in the semaglutide arm, which were not adequately explained in the resubmission. The use of endpoint utility values for responders and non-responders in the model was inappropriate as it did not account for these baseline differences.</p> <p>For many of the subgroups, weight loss non-responders in the semaglutide arm achieved similar, or in some cases even larger, improvements in utility values compared to weight loss responders. These results were not consistent with weight loss being the main driver of utility gains.</p>	High, favours semaglutide

Source: Constructed during the evaluation.

6.65 During the evaluation, the base case analysis was corrected and updated with the following changes:

- The formula calculating the utility values of non-responders in the semaglutide arm was corrected to reference the non-responder utility. The PSCR acknowledged this error.

- The formula calculating trial persistence estimates in the semaglutide arm was corrected to allow the total number of discontinuing patients to accumulate. The PSCR acknowledged this error.
- The effective price for semaglutide was recalculated based on the updated pricing provided by the sponsor, using the standard method for determining effective DPMQs.
- The MBS fees were updated to reflect the August 2023 Schedule.

6.66 The corrected results of the modelled economic evaluation are summarised in Table 14.

Table 14: Results of the economic evaluation

Component	Semaglutide	Placebo	Increment
Modelled analysis using trial duration (68 weeks; no discounting)			
Costs		\$2,120	
QALYs	0.8786	0.7935	0.0852
Incremental cost per QALY gained			¹
Modelled analysis with 5 year time horizon (discounted)			
Costs		\$3,020	
QALYs	3.0927	2.7874	0.3053
Incremental cost per QALY gained			²

Source: Table 3-8, p184 of the resubmission; with recalculations based on semaglutide Section 3 Workbook (July 2023) Excel spreadsheet
Abbreviations: QALY, quality adjusted life years

Note: The resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$25,000 to < \$35,000

6.67 Based on the economic model, treatment with semaglutide was associated with an incremental cost per QALY gained of \$25,000 to < \$35,000 compared to placebo for the management of severe obesity (uncorrected estimate: \$15,000 to < \$25,000 per QALY gained). The estimated cost-effectiveness of semaglutide in the current resubmission (\$25,000 to < \$35,000 per QALY gained) is substantially higher than the estimate originally proposed in the March 2022 submission (\$15,000 to < \$25,000 per QALY gained), although the PBAC noted that the March 2022 estimate should not be considered reliable due to a number of calculation errors, logical inconsistencies and unsupported values (para 7.9, semaglutide PSD, March 2022 PBAC meeting).

6.68 For every 1,000 patients treated with semaglutide versus placebo and followed up for 5 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- Improved quality of life associated with weight loss (average increase of 0.3362 quality-adjusted life years per patient).
- Reduced time spent with pre-diabetes (average decrease of 0.7126 years per patient).

- Increased incidence of serious adverse events (18 additional events).
- Additional drug and weight management costs of \$10.3 million.

6.69 The results of the sensitivity analyses, presented in Table 15, indicate that the model is most sensitive to treatment arm utility values, responder status utility values and the semaglutide drug price. However, it should be noted that the impact of multiple episodes of care (i.e. semaglutide re-treatment), maintenance of treatment effects over time (despite decreased longer-term use of adjunctive weight management), use of alternative stopping rules, and different utility sets could not be adequately assessed using the current economic model.

Table 15: Results of key univariate sensitivity analyses (corrected)

Analyses	Incremental cost (\$)	Incremental QALY	ICER	Change from base case ICER (%)
Base case	█	0.3053	█ ¹	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate	█	0.3140	█ ¹	-
0% discount rate	█	0.3362	█ ¹	-
Time horizon (base case: 5 years)				
3 years	█	0.1917	█ ¹	+
10 years	█	0.5072	█ ¹	-
Utility values (base case: variable with time and treatment arm based on subgroup analyses of the STEP-1 trial; extrapolated between Week 68 and Week 104 assuming constant treatment arm utilities; extrapolated beyond 104 weeks based on end-of-trial values by weight responder status regardless of treatment arm)				
Increase treatment difference in utility values to upper 95% CI at all timepoints using semaglutide as anchor	█	0.4011	█ ²	-
Decrease treatment difference in utility values to lower 95% CI at all timepoints using semaglutide as anchor	█	0.2095	█ ³	+
Switch to responder analysis after Week 68	█	0.3162	█ ¹	-
Use responder status values based on change from baseline	█	0.2326	█ ³	+
Costs (base case: resource use and unit costs based on various sources)				
Use effective DPMQs proposed by sponsor	█	0.3053	█ ¹	+
Use semaglutide effective price for diabetes for all dose strengths	█	0.3053	█ ⁴	-

Source: 3-11, p185 of the resubmission; with recalculations based on semaglutide Section 3 Workbook (July 2023) Excel spreadsheet
 Abbreviations: CI, confidence interval; DPMQ, dispensed price for maximum quantity; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Note: The resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

⁴ \$5,000 to < \$15,000

6.70 The results of multivariate sensitivity analyses using different patient populations are summarised in Table 16. During the evaluation, these analyses were modified to use the change in utility score rather than the endpoint utility score for responders and non-responders due to the large differences in baseline utility values between these groups, resulting in a modified base case ICER of \$35,000 to < \$45,000/QALY gained.

The PSCR contended that, in the extrapolated period of the model, it was reasonable to apply utilities based on response status rather than treatment allocation, as it attempted to reflect the impact of the proposed PBS treatment stopping rule. The ESC agreed with evaluation and considered the large differences in baseline utility values should be factored in rather than relying on the endpoint utility. The pre-PBAC response suggested it would be appropriate to use a change from baseline to final utility value approach for responders and non-responders in each of the semaglutide and placebo groups as opposed to a single approach encompassing both groups. The ICER obtained from this revised analysis, for the proposed base case population and restriction is \$25,000 to < \$35,000. However, review of this method suggested it is not appropriate as it assumes that patients who have trialled and failed semaglutide (non-responder utility: 0.6587) will retain a utility improvement over equivalent placebo patients (non-responder utility: 0.5845) for the remaining five years of the model despite neither group receiving ongoing treatment with semaglutide. This is a very strong bias in favour of semaglutide (additional benefit without additional cost) which substantially reduces the estimated ICER per QALY gained.

Table 16: Results of multivariate sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	Change from base case ICER (%)
Base case		0.3053	¹	-
Modified base case with responder status utility values based on change from baseline		0.2326	²	+
Patient population (base case: patients with BMI ≥40 kg/m² and ≥2 weight-related comorbidities with OSA, KOA or PD)				
ITT population		0.1483	³	+
BMI ≥35 kg/m ² & ≥1 weight-related comorbidity		0.1910	⁴	+
BMI ≥35 kg/m ² and ≥2 weight-related comorbidities with OSA or KOA		0.1326	⁵	+
BMI ≥40 kg/m ² and ≥1 weight-related comorbidity with OSA or KOA		0.2006	⁴	+
BMI ≥40 kg/m ² and ≥2 weight-related comorbidities with OSA or KOA		0.1937	⁴	+

Source: 3-11, p185 of the resubmission; with recalculations based on semaglutide Section 3 Workbook (July 2023) Excel spreadsheet
 Abbreviations: BMI, body mass index; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; KOA, knee osteoarthritis; OSA, obstructive sleep apnoea; PD, pre-diabetes; QALY, quality adjusted life year

Note: During the evaluation, these analyses were modified to use the change in utility score rather than the endpoint utility score for responders and non-responders due to the large differences in baseline utility values between these groups.

Note: The resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

³ \$75,000 to < \$95,000

⁴ \$45,000 to < \$55,000

⁵ \$55,000 to < \$75,000

6.71 The results of the multivariate sensitivity analyses indicate that the model is highly sensitive to different patient populations, primarily due to differences in treatment

arm utility values, response status utility values and the proportion of treatment responders.

Drug cost/patient/year

6.72 The estimated drug costs per patient per year are summarised in Table 17.

Table 17: Calculation of drug cost per year

	STEP-1	Economic model	Financial estimates
Dose distribution at end of dose titration	Lower doses: 16.5% 2.4 mg: 83.5%	1.7 mg: 0% 2.4 mg: 100%	1.7 mg: 0% 2.4 mg: 100%
Dose distribution on maintenance therapy ^a	Lower doses: 10.4% 2.4 mg: 89.6%	1.7 mg: 0% 2.4 mg: 100%	1.7 mg: 5% 2.4 mg: 95%
Cost per 28 days (effective DPMQ) (\$)	-	0.25 to 1.0 mg: █ 1.7 to 2.4 mg: █	0.25 to 1.0 mg: █ 1.7 to 2.4 mg: █
Adherence	NR	100%	100%
Cost per year ^b	-	Year 1: █ Year 2+: █	Year 1: █ Year 2+: █
Proportion of patients on treatment ^c	18.0% of patients discontinued treatment over 68 weeks.	Year 1: 85.8% Year 2: 55.8% Year 3: 53.0% Year 4: 50.4% Year 5: 47.9% Year 6: NA	Year 1: 100% Year 2: 58.0% Year 3: 55.1% Year 4: 52.3% Year 5: 49.7% Year 6: 47.2%

Source: constructed during the evaluation using Section 3 Workbook (July 2023) and Section 4 Workbook (July 2023) Excel spreadsheets
Abbreviations: DPMQ, dispensed price for maximum quantity; NA, not applicable; NR, not reported

^a Dose distribution on maintenance therapy for the STEP-1 target subgroup population was based on the proportion of patients using the maximum dose of 2.4 mg at the end of the trial.

^b Cost per year for persistent patients.

^c Based on proportion on treatment at the end of each year. For the economic model, estimates incorporate discontinuation due to death. For the financial estimates, estimates are based on a fixed cohort from Year 1.

Note: The resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods.

6.73 The resubmission did not adequately justify the differences in semaglutide dose distribution and treatment persistence between different sections of the document.

6.74 The estimated utilisation of adjunctive weight management is summarised in Table 18. In the STEP-1 trial, patients received counselling administered by a dietician (or similar healthcare professional) every 4 weeks. Compliance to adjunctive care in the STEP-1 trial was not available.

Table 18: Health resource utilisation for adjunctive weight management

	Economic model		Financial estimates	
	Semaglutide	Placebo	Semaglutide	Placebo
Year 1				
TCA visits	4 (baseline; weeks 16, 28, 44)		4	2.8
GP visits	3 (for titration)	0	3 (for titration)	0
Dietician/exercise physiologist	14 (baseline and every 4 weeks)		16	13.6
Year 2				
TCA visits	1 (in week 68)		2	1.4
GP visits	2 (in week 68, 92)		0	0
Dietician/exercise physiologist	7 (1 in week 56, 60, 64; 2 in week 68; 2 in week 92)		4	2.8
Year 3+				
TCA visits	1.1 per year (1 every 48 weeks)		2	1.4
GP visits	1.1 per year (1 every 48 weeks)		0	0
Dietician/exercise physiologist	4.3 per year (2 every 24 weeks)		4	2.8
Proportion of patients on treatment ^a	Year 1: 85.8%	Year 1: 80.6%	Year 1: 100%	Year 1: 100%
	Year 2: 55.8%	Year 2: 11.8%	Year 2: 58.0%	Year 2: 58.0%
	Year 3: 53.0%	Year 3: 11.2%	Year 3: 55.1%	Year 3: 55.1%
	Year 4: 50.4%	Year 4: 10.6%	Year 4: 52.3%	Year 4: 52.3%
	Year 5: 47.9%	Year 5: 10.1%	Year 5: 49.7%	Year 5: 49.7%
	Year 6: NA	Year 6: NA	Year 6: 47.2%	Year 6: 47.2%

Source: constructed during the evaluation using Section 3 Workbook (July 2023) and Section 4 Workbook (July 2023) Excel spreadsheets
Abbreviations: GP, general practitioner; NA, not applicable; TCA, team care arrangements

^a Based on the proportion on treatment at the end of each year. For the economic model, estimates incorporate discontinuation due to death. For the financial estimates, estimates are based on a fixed cohort from Year 1.

6.75 Estimates of utilisation of MBS services were not consistent between the economic model and the budget impact model due to differences in the initial treatment period (68 weeks in the economic model versus 1 year in the financial estimates) and differences in the ongoing review of continuing patients (alternating team care reviews and GP consultations in the economic model versus team care reviews only in financial estimates). The estimates are inappropriate as they do not account for limitations to the use of some MBS items (i.e. maximum 5 visits per year shared between allied health providers) and assumed that the semaglutide-specific circumstances of use (e.g. treatment response) also apply to adjunctive weight management.

Estimated PBS usage & financial implications

6.76 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing semaglutide for patients with BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities with obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. Key inputs relied on in the financial estimates are summarised in Table 19 below.

Table 19: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value applied and source	Commentary on the resubmission	DUSC comments
Eligible population			
Australian adult population with BMI ≥ 40 kg/m ²	From 832,310 in Year 1 to 892,213 in Year 6. Based on the Australian National Health Survey 2017-2018 with estimates based on Australian adult population projections.	DUSC previously noted that growth in the Australian obese population is increasing beyond population growth, based on National Health Survey data indicating the proportion of Australian adults categorised as obese increased from 27.9% in 2014-15 to 31.3% in 2017-18. The population estimates do not account for lower BMI thresholds in Asian or Aboriginal or Torres Strait Islander populations.	DUSC considered the assumption of adults with a BMI ≥ 40 kg/m ² based only on population growth to be conservative. DUSC noted the increasing prevalence of obesity and cardiovascular disease were not accounted for in this parameter.
Obese patients with multiple comorbidities without diabetes	30.3% based on the Australian National Health Survey 2017-2018. Based on 44.2% with BMI ≥ 40 kg/m ² who have at least two long term health conditions (including arthritis; asthma; back problems; cancer; chronic obstructive pulmonary disease; diabetes; hay fever and allergic rhinitis; heart, stroke and vascular disease; hypertension; kidney disease; mental and behavioural conditions; and osteoporosis). The resubmission then subtracted the 13.9% of patients with BMI ≥ 40 kg/m ² who have diabetes.	The long-term health conditions in the ABS data do not match the weight-related comorbidities in the requested restriction (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). In particular, the ABS estimates do not include pre-diabetes and dyslipidaemia which are likely to be highly prevalent conditions in this population and is also confounded by the inclusion of other health issues such as mental and behavioural conditions which are not components of the requested restriction. Subtracting the diabetes estimate from the obese population with multiple comorbidities estimate inappropriately assumes that all patients with diabetes have multiple comorbidities.	DUSC considered this assumption to be highly uncertain. DUSC considered this parameter could be underestimated as patients with pre-diabetes were excluded from the ABS estimates. DUSC noted mental health was not listed as a weight related comorbidity in the proposed PBS restriction. DUSC considered that comorbidities in the restriction including menstrual disorder, involuntary impaired infertility, asthma, chronic obstructive pulmonary disease, hyperuricaemia or gout may not be appropriate and may add significant uncertainty to the estimates. DUSC considered that fewer comorbidities which were better targeted to the population and better defined would reduce the uncertainty. DUSC noted the financial estimates were sensitive to this assumption.
Obese, nondiabetic patients with multiple comorbidities including OSA, KOA or PD	84.5% based on the STEP-1 trial. Based on the proportion of patients with BMI ≥ 40 kg/m ² and ≥ 2 comorbidities who have any of the three specified conditions (obstructive sleep apnoea, knee osteoarthritis, pre-diabetes).	The applicability of this estimate to the Australian population was unclear but there are unlikely to be any other relevant data sources to inform this estimate given the highly defined population proposed in the resubmission.	DUSC considered this assumption to be reasonable given the lack of alternative data sources; but subject to the above-noted poorly defined co-morbidity list. DUSC noted the financial estimates were sensitive to this assumption.

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Data	Value applied and source	Commentary on the resubmission	DUSC comments
Initiation rate	From 80% in Year 1 to 50% in Years 4-6. Initial uptake rates were assumed based on market experience in the US and factoring in the severity of the target population, limited subsidised weight management care and substantial (social) media attention. The resubmission assumed a declining initiation rate over time.	The estimated initiation rate is inherently uncertain although it appears reasonable to assume a very high initial uptake. There are currently no data to suggest a waning in demand over time.	DUSC noted no data was provided to support the submission's assumptions regarding treatment uptake rates. DUSC agreed with the commentary that there would likely be high initial uptake of semaglutide due to the high unmet demand. DUSC considered the assumption of the waning demand over time to be uncertain. DUSC considered that a grandfather clause would add significant uncertainty to the initiation rates.
Response rate at Week 68	58% based on the STEP-1 trial. Based on the proportion of patients achieving $\geq 10\%$ weight loss at Week 68 in the patient subgroup with BMI ≥ 40 kg/m ² and ≥ 2 weight-related comorbidities with obstructive sleep apnoea, knee osteoarthritis or pre-diabetes	The real-world effectiveness of semaglutide in clinical practice compared to the reported efficacy in clinical trial settings is unclear given the potential for differences in circumstances of use (e.g. suboptimal compliance to semaglutide and/or adjunctive weight management).	DUSC considered the effectiveness of semaglutide would likely be less in clinical practice compared to clinical trials. However, DUSC considered the threshold for which clinicians decide to cease treatment may be different in clinical practice.
Treatment persistence	Assumed 100% in first 2 years with no justification, assumed 95% in subsequent years on the basis that it was reasonable to expect high levels of persistence in patients achieving a clinical response to treatment.	The first and second year persistence estimates were inconsistent with the economic model, which allowed patients to discontinue therapy during this period. The treatment persistence assumptions were substantially higher than observed in the STEP-1 clinical trial (annual discontinuation rate of 15.2% in the semaglutide arm). Evidence from observational studies of treatment persistence with semaglutide in type 2 diabetes (Uzoigwe 2021, Mody 2022) as well as other medications for the management of obesity (Ganguly 2018, Ahmad 2021) suggest substantially lower treatment persistence estimates in clinical practice.	DUSC considered treatment persistence may be overestimated, however patients would be more likely to re-initiate treatment in clinical practice compared to in clinical trials. DUSC also commented that the 2-year discontinuation rule would be likely to increase persistence and may lead to inappropriate prescribing and potential usage of semaglutide in patients who would not otherwise qualify for the therapy.
Treatment utilisation			
Treatment adherence	100%. Assumed	The assumption that all patients would titrate to the highest dose was inconsistent with data from the STEP-1 trial which indicated that 16.5% of patients had not achieved the maximum dose at the end of the titration period. The assumption that all patients would be fully adherent with therapy is unlikely to be representative of clinical practice.	DUSC commented that achieving target doses with medications requiring up titration of doses is almost always higher in clinical trials than clinical practice and noted the gastrointestinal events associated with semaglutide.

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Data	Value applied and source	Commentary on the resubmission	DUSC comments
Distribution of continuing scripts	Distribution of continuing scripts was assumed. 1.7 mg: 5% 2.4 mg: 95%.	This assumption was inconsistent with data from the STEP-1 trial that indicated that 10.4% were using less than the maximum dose at the end of the trial.	DUSC considered the assumption that 2.4 mg dose would account for 95% of prescriptions to be significantly overestimated.
MBS services			
MBS services per semaglutide patient	Assumption. Assumed all semaglutide patients would be subject to a team care arrangement (MBS 723) that would be regularly reviewed with 3 visits in the first year and then 2 visits per year in subsequent years (MBS 732). Assumed 3 additional GP visits (MBS 23) for dose titration. Assumed 16 allied health visits (10953/10954) in the first year, based on the STEP-1 trial protocol (which was based on 68 weeks), and 4 visits per year in subsequent years.	Estimates of MBS services were not consistent between the economic model and the budget impact model due to differences in the initial treatment period (68 weeks vs 1 year) and differences in the ongoing review of continuing patients (alternating team care reviews and GP consults vs. team care reviews only). The assumption that all patients would be subject to a team care arrangement was inconsistent with the proposed restriction which specifically does not include a requirement for patients to be managed through a team care arrangement in order to allow for flexibility in delivery. The resubmission did not account for the limit of 5 allied health visits (e.g. 10953/10954) per year under team care arrangements. The utilisation of MBS items 10953 (exercise physiology) and 10954 (dietetics services) for the narrow target population in the budget impact analysis exceeds the current utilisation of these items for the whole Australian population (including other higher risk groups such as cardiovascular disease, diabetes and the broader obesity population). There are no data to support the level of adjunctive weight management care required with longer-term semaglutide treatment.	DUSC noted that these estimates would overwhelm existing service availability and thus are uncertain.
MBS services per standard care patient	Assumption. The resubmission noted that standard care may be sub-optimal in practice and estimated use of team care arrangements based on 70% of the level estimated for semaglutide and estimated allied health use based on 70-85% of the level estimated for semaglutide.		

Source: Table 18, pp32-34 of the commentary on the resubmission.

Abbreviations: ABS, Australian Bureau of Statistics; AEMP, approved ex-manufacturer price; BMI, body mass index; DPMQ, dispensed price for maximum quantity; DUSC, Drug Utilisation Sub-Committee; KOA, knee osteoarthritis; MBS, Medicare Benefits Schedule; OSA, obstructive sleep apnoea; PBS, Pharmaceutical Benefits Scheme; PD, pre-diabetes; RPBS, Repatriation Pharmaceutical Benefits Scheme

6.77 The estimated utilisation and financial implications (using the effective DPMQ) of a PBS listing of semaglutide for severe obesity is summarised in Table 20 below.

6.78 During the evaluation, a major calculation error was identified in the estimated number of scripts for treatment initiators, which was based on 4.43 scripts per patient rather than 13 scripts per patient (e.g. 170,647 treatment initiators in Year 1 used a total of 24,378 scripts of the initial 0.25 mg semaglutide dose) due to the incorrect application of population split estimates in the Excel spreadsheet. This error was corrected during the evaluation.

6.79 A number of other smaller calculation errors were also corrected during the evaluation.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	2	1	1	1	1
Number of scripts dispensed	3	4	4	4	4	3
Cost to PBS/RPBS less co-payments	4	4	5	5	4	4
Cost to MBS	6	7	8	8	7	7
Net cost to PBS/RPBS/MBS	4	4	5	5	4	4
Previous submission (March 2022)						
Number of patients treated	2	9	10	11	12	13
Number of scripts dispensed	3	14	15	16	17	18
Cost to PBS/RPBS less co-payments	19	20	20	20	20	20

Source: Table 19, p35 of the commentary on the resubmission.

Note: The resubmission used a non-standard method of calculating effective DPMQs from effective AEMPs which did not account for the differences in fees and markups for the published and effective DPMQs. During the evaluation the effective DPMQs were recalculated using standard methods.

The redacted values correspond to the following ranges

- 1 100,000 to < 200,000
- 2 200,000 to < 300,000
- 3 2,000,000 to < 3,000,000
- 4 \$400 million to < \$500 million
- 5 \$300 million to < \$400 million
- 6 \$50 million to < \$60 million
- 7 \$20 million to < \$30 million
- 8 \$10 million to < \$20 million
- 9 300,000 to < 400,000
- 10 400,000 to < 500,000
- 11 500,000 to < 600,000
- 12 600,000 to < 700,000
- 13 700,000 to < 800,000
- 14 4,000,000 to < 5,000,000
- 15 6,000,000 to < 7,000,000
- 16 7,000,000 to < 8,000,000
- 17 8,000,000 to < 9,000,000
- 18 9,000,000 to < 10,000,000
- 19 \$800 million to < \$900 million
- 20 > \$1 billion

6.80 The estimated cost to the PBS/RPBS of listing semaglutide for obesity ranged from \$300 million to < \$400 million to \$400 million to < \$500 million per year, with a cumulative total of > \$1 billion over the first 6 years of listing (uncorrected estimate > \$1 billion over the first 6 years).

6.81 The estimated MBS costs associated with listing semaglutide for obesity ranged from \$10 million to < \$20 million to \$50 million to < \$60 million per year, with a cumulative

total of \$100 million to < \$200 million over the first 6 years of listing (uncorrected estimate \$100 million to < \$200 million over the first 6 years).

- 6.82 The estimated PBS/RPBS cost in the current resubmission was substantially lower than in the March 2022 submission (previously >\$1 billion over 6 years) primarily due to the smaller treated population as well as a reduction in the effective price of semaglutide (previously \$| per script for all dose strengths). The March 2022 submission assumed that the listing of semaglutide would not substantially affect the use of MBS items (i.e. dietician visits) for the management of obesity.
- 6.83 DUSC noted in Years 3 and 4 of listing the net cost to government decreased to \$300 million to < \$400 million and \$300 million to < \$400 million, respectively. DUSC noted this was likely due to the number of initiating patients decreasing, as well as the stopping rule in the continuing restriction. The financials lacked face validity due to fluctuating numbers.
- 6.84 DUSC considered the estimates presented in the resubmission to be uncertain. The main issues were:
- There were significant uncertainties regarding the size of the obese population with BMI > 40 g/m², the proportion of those patients meeting the additional comorbidity criteria, the expected initiation rate as well as treatment persistence and treatment effectiveness in clinical practice.
 - The comorbidities in the restriction, based on the STEP-1 clinical trial and seemingly selected based upon response rates to quality of life questionnaire, were considered too diverse and ill-defined and may not ensure either optimal targeting of the patient group most likely to benefit and being so broad would add significant uncertainty in the financial estimates.
 - The inclusion in the proposed PBS restriction of a discontinuation requirement for 2 years after cessation of semaglutide was not considered to be appropriate. Findings from the STEP-1 extension trial has shown weight regression following cessation of semaglutide treatment and this would adversely affect both the health-related quality of life (HRQoL) benefits and the downstream benefits (including potential effects on cardiovascular outcomes) associated with weight loss.
 - The inclusion of a 2-year discontinuation requirement would also have a significant impact on the financial estimates and would also increase the likelihood of inappropriate prescribing and utilisation.
 - The likelihood of utilisation outside the requested PBS population is estimated to be high, given that the clinical trial evidence and treatment guidelines support use in broader populations and the widespread publicity and interest in weight loss pharmacotherapy especially the GLP-I RAs.

- A Risk Sharing Arrangement would be necessary given the uncertainties in estimating the utilisation and financial implications of the requested PBS listing of semaglutide for severe obesity.

Quality Use of Medicines

- 6.85 The resubmission stated that the sponsor will undertake pharmacovigilance activities and provide education support to patients, doctors, pharmacists and other healthcare professionals.
- 6.86 The patient support program is still being developed but will include an online platform to support, educate and motivate patients and manage their expectations to help ensure a positive experience with semaglutide. The resubmission claimed that the patient support program is designed to empower patients so that they are better prepared to control their weight throughout their weight loss journey. It was unclear whether the proposed patient support program included individual counselling on diet and exercise.
- 6.87 There is a risk of diversion of semaglutide (e.g. patients on-selling their prescribed medications) given the high demand for semaglutide as a weight loss therapy, narrow proposed PBS restriction and potential for profiteering from the difference between the patient co-payment and private market price of semaglutide.
- 6.88 The availability of semaglutide for obesity may exacerbate existing equity of access issues for patients accessing subsidised weight management care. The PSCR contented that as semaglutide is expected to be prescribed in primary care settings, it should result in reduced pressure on specialist weight services.
- 6.89 The DUSC reemphasised prior comments in the consideration of the March 2022 submission regarding the limited details of a multimodal program for weight management as well as the potential costs and allied health capacity to support a multimodal program.

Financial Management – Risk Sharing Arrangements

- 6.90 The resubmission did not propose a Risk Sharing Arrangement. However, the March 2022 submission acknowledged that the magnitude of expected financial impact and uncertainty around the total impact means that a Risk Sharing Arrangement will be necessary.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of semaglutide for the treatment of severe obesity. The PBAC considered that the resubmission did not adequately support access to semaglutide as defined in the proposed PBS population. There was no strong clinical rationale for the obesity comorbidities selected for inclusion in the proposed PBS listing and they did not identify patients most likely to experience relatively large

reductions in weight or long-term benefits from weight loss. No new clinical trial evidence was presented in this resubmission to support benefits of longer-term use, although the Committee noted that new randomised controlled trial data highlighting potential benefits in reducing cardiovascular events was announced by the sponsor in a press release after the resubmission was received. The PBAC considered this information would be informative in defining eligible patients who would obtain downstream health benefits of weight loss. The PBAC also considered it would be unreasonable for patients currently eligible for semaglutide 1 mg once weekly (Ozempic®) for Type 2 diabetes, who had severe obesity, to not be able to access the higher dose of semaglutide 2.4 mg once weekly (Wegovy®) and advised that this patient group be included for future consideration. The PBAC considered semaglutide was not cost effective at the price proposed, noting although only short-term weight loss benefits were modelled, there were multiple issues with the utility values applied. The PBAC considered a Risk Sharing Arrangement (RSA) would be required given the extremely high estimated expenditure and the criteria for defining the patient population. The PBAC advised a facilitated resolution pathway would be appropriate given the high added therapeutic value of semaglutide and outstanding issues for resolution in defining the patients in whom treatment would reduce downstream consequences of obesity, be cost-effective, and appropriate for the significant Government expenditure.

- 7.2 The PBAC recognised the high burden of disease in Australia, acknowledging the high and urgent unmet clinical need for effective weight loss strategies for severe obesity. The PBAC welcomed the input from a large number of consumers and clinicians, as well as professional and patient organisations, that showed strong and consistent support for widespread use of semaglutide.
- 7.3 The PBAC recalled its initial consideration of semaglutide in March 2022 was for a broader population, with numerous qualifying comorbidities, and it had advised a more targeted approach would be necessary to assure cost-effectiveness based on the STEP trials (para 3.5, semaglutide PSD, March 2022 PBAC meeting). The PBAC acknowledged the approach taken in this resubmission was in line with its previous advice to focus on the short-term benefits of weight loss given the limitations of the data (see paragraph 1.3). Although this resubmission selected a subgroup of patients from the STEP-1 trial intending to identify patients who may be more likely to achieve quality of life improvements from weight loss over the short-term, the analyses based on this approach did not provide a strong clinical rationale for the chosen comorbidities for eligibility, which included two weight-related comorbidities, with at least one of obstructive sleep apnoea, knee osteoarthritis or pre-diabetes. Moreover, given the time between submissions and the reporting of headline results from the SELECT trial, the PBAC considered it has become clear that the added therapeutic value of semaglutide therapy is for treating patients at high cardiometabolic risk who are most likely to achieve long term benefits from weight loss.
- 7.4 The PBAC noted and acknowledged the submission approach to defining a more

targeted population, the ESC and DUSC advice which provided alternative approaches and raised opposing views to the submission, and the frustration in the pre-PBAC response regarding the unclear path forward to the optimal clinical place for semaglutide. The PBAC discussed the purpose of indications is to identify the patient populations in whom the intervention is most likely to benefit and be cost-effective. The Committee determined the appropriate clinical place for semaglutide could be defined using co-morbidities and other risk factors on the causal pathway of cardiometabolic disease, was broadly consistent with the SELECT trial inclusion criteria and endpoints evaluated, would be consistent with the intent of the submission, and address uncertainty in the incremental cost effectiveness. A revised restriction could include patients with BMI ≥ 40 kg/m² (or 37 kg/m² for patients with Asian or Aboriginal or Torres Strait Islander ethnicity) with either pre-existing cardiovascular disease, type 2 diabetes, or at least 2 weight-related comorbidities that characterise metabolic syndrome/high cardiometabolic risk (hypertension, dyslipidaemia, chronic kidney disease, fatty liver disease, pre-diabetes).

- 7.5 In addition, the PBAC acknowledged the disproportionate burden of chronic disease in the Aboriginal and/or Torres Strait Islander population and agreed with the ESC that identifying as an Aboriginal and/or Torres Strait Islander person could also be one of the eligibility criteria (see paragraph 3.10).
- 7.6 The PBAC advised the assessment of weight loss for continuing therapy should be done at 52 weeks, rather than 68 weeks as proposed in the resubmission. The PBAC noted the change in body weight over time with and without treatment in the STEP-1 extension study showed that the difference between weeks 52 and 68 appeared negligible and the cost of an additional 16 weeks treatment would not be justified in patients who did not achieve at least 10% weight loss by week 52 (see Figure 1 semaglutide PSD, March 2022 PBAC meeting (sourced from Figure 14.2.9 (p 137) of the STEP-1 extension report)).
- 7.7 The PBAC also noted the intent of the 2-year treatment break for patients that discontinue therapy, however, the PBAC considered this would be difficult to effectively implement in clinical practice and did not consider the 2-year wait before retreatment was required.
- 7.8 The PBAC considered the appropriate line of therapy was after inadequate weight loss from previous lifestyle-based weight management. However, it was noted that dietetic advice was unlikely to be widely available to patients, and the wording of the criteria for ongoing adjunctive lifestyle-based weight management would need reconsideration to remove the specification of how it is managed.
- 7.9 The PBAC reaffirmed its previous view 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 to bariatric surgery in Australia. The PBAC noted that the TGA had accepted an application for tirzepatide as ‘an adjunct to a reduced-calorie diet and increased physical activity for chronic weight

management'. This may be a relevant comparator for a future resubmission for semaglutide.

- 7.10 The PBAC recalled it had previously accepted the superior comparative effectiveness claim with regards to surrogate markers of weight loss, HbA1c and other biomarkers, but that effectiveness of clinical endpoints remained uncertain paragraph 7.7, semaglutide PSD, March 2022 PBAC meeting). The PBAC noted the resubmission presented extensive new *post hoc* subgroup analyses of the STEP-1 trial. The PBAC noted the ESC concerns regarding the robustness of these analyses given the subgroup populations were identified *post hoc*, patient allocation to treatment arms was not stratified based on the nominated variables and many of the analyses were based on small patient numbers with notable and potentially important imbalances in patient characteristics between treatment arms at baseline (see paragraph 6.47). The PBAC noted the selection of subgroups to present in the resubmission was based on transformation of SF-36 questionnaire results into SF-6D health states and a scoping exercise was undertaken by the sponsor to assess the response across subgroups defined by baseline BMI category, number and type of weight related comorbidities, and key demographic characteristics. Although the proposed subgroup for the submission base case may have represented the largest incremental response based on quality of life outcomes over the trial period (for patients with BMI ≥ 40 kg/m²), the PBAC noted the results presented in Table 5, Table 6 and Table 7 demonstrated that the selected comorbidities were not treatment effect modifiers and there were no important differences in the absolute and relative effects on weight loss across the subgroups. The magnitude of difference between treatments for weight loss was generally smaller in the subgroup populations compared to the ITT population. Ultimately, the PBAC considered there was no strong rationale for selecting these subgroups and overall, despite these new analyses, the PBAC did not consider the optimal target population for semaglutide could be adequately identified from this approach.
- 7.11 The PBAC noted the top-line results from the SELECT trial which were released by the sponsor via press release, indicated that semaglutide treatment was associated with a 20% relative risk reduction in major cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) compared to placebo in overweight/obese patients with established cardiovascular disease. The PBAC acknowledged the positive results, however, given the trial had not been published in a peer-reviewed journal or provided for evaluation, it could not comment further on the significance of the outcomes. The PBAC did, however, consider the top line results relevant for identifying a clinically appropriate targeted population for potential PBS subsidy.
- 7.12 The PBAC noted the appreciable gastrointestinal side effects which lead to discontinuation of treatment in more than 5% of patients in the selected subgroup. The PBAC reaffirmed its previous view that the claim of inferior comparative safety was reasonable (paragraph 7.8, semaglutide PSD, March 2022 PBAC meeting).

- 7.13 The PBAC noted the new economic model developed for this resubmission was based on a cost-utility analysis of semaglutide vs placebo for an initial episode of care for the severe obesity subgroup from the STEP-1 trial (baseline BMI ≥ 40 kg/m² and ≥ 2 weight-related comorbidities), over 5 years. The PBAC noted the ICER for the evaluator corrected model was \$25,000 to < \$35,000/QALY gained and that this increased to \$35,000 to < \$45,000/QALY gained with more appropriate modelling of utilities for responder status based on change from baseline. The PBAC noted the alternative approach and ICER provided in the pre-PBAC response but expected that this was likely biased in favour of semaglutide (see paragraph 6.70). Overall, the PBAC noted the multiple issues identified during evaluation regarding the utility values and that alternative utility sets and maintenance of treatment effects over time (despite decreased longer-term use of adjunctive weight management) could not adequately be assessed using the current model (see paragraph 6.69).
- 7.14 The PBAC noted the ESC advice that modelling QoL improvement from weight loss rather than extrapolating long-term benefits was a potentially valid approach (noting results of the HILDA survey (2022)⁵), however, the model provided in this resubmission was unreliable and produced higher ICERs than accepted in previous recommendations for therapies in chronic conditions, such as evolocumab in atherosclerotic cardiovascular disease. The PBAC expected that modelling downstream benefits should now be possible given the results of the SELECT trial are available and that this may overcome the issues raised in the March 2022 submission and this resubmission with regards to modelling based on surrogate outcomes of weight loss.
- 7.15 The PBAC noted the issues raised in the DUSC advice included uncertainty regarding the size of the population, particularly given the diverse and ill-defined comorbidities, uncertain estimates of initiation and persistence, potential use outside the proposed restriction and the need for an RSA. The PBAC also noted the impact that the 2-year treatment break for patients that discontinue therapy would have on reducing the financial implications over 6 years and the DUSC concern that this treatment break may incentivise inappropriate use and prescribing. As noted in paragraph 7.7, the PBAC did not consider the treatment break was required. The PBAC advised substantial revision of the estimated utilisation would be required to accommodate a revised place in therapy in accordance with paragraphs 7.4 to 7.8).
- 7.16 The PBAC considered semaglutide addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies. However, the PBAC considered a number of issues

⁵ Keramat SA, Alam K, Keating B, et al. Morbid obesity, multiple long-term conditions, and health-related quality of life among Australian adults: Estimates from three waves of a longitudinal household survey. *Prev Med Rep.* 2022; 28:101823. Published 12 May 2022. <https://doi.org/10.1016/j.pmedr.2022.101823>

remained outstanding. Before a resubmission for semaglutide is made, the PBAC would like to offer the sponsor a solution-focussed workshop with one or more members of the PBAC, to explore feasible options to address the following issues:

- Redefining the place in therapy based on co-morbidities and other risk factors on the causal pathway of cardiometabolic disease
- Data available to support the redefined clinical place, including the SELECT trial, STEP-2 trial (in T2DM patients), and other outcomes data if available to supplement the STEP trials
- Revised economic model including long-term benefits from the SELECT trial
- Revised financial implication and options for an RSA.

The workshop agenda would be based on the issues for resolution outlined above. Should the sponsor accept this offer, a facilitated resolution pathway may be acceptable for the resubmission (as defined in the *Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme*). It should be noted that any advice provided by members of the PBAC, the sponsor or the department in a workshop is in no way binding on the PBAC, the department, sponsor, evaluation groups or sub-committees of the PBAC. If this option is not acceptable to the sponsor, a standard re-entry pathway is available.

7.17 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

Novo Nordisk is disappointed with the outcome and appreciates all 146 submissions from individuals, healthcare professionals and organisations in support of making Wegovy® available on the PBS for the treatment of obesity. Novo Nordisk remains committed to continuing to work collaboratively with the PBAC to ensure Australians living with obesity, especially high-risk and vulnerable patients, have government-funded access to Wegovy®.