7.04 SEMAGLUTIDE,
Solution for injection 0.25 mg in 0.5 mL single dose pre-filled pen,
Solution for injection 0.5 mg in 0.5 mL single dose pre-filled pen,
Solution for injection 1 mg in 0.5 mL single dose pre-filled pen,
Solution for injection 1.7 mg in 0.75 mL single dose pre-filled pen,
Solution for injection 2.4mg in 0.75mL single dose pre-filled 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 treatment initiation and grandfathering, as well as a Streamlined Authority listing for treatment continuation of semaglutide in patients with established cardiovascular disease (eCVD) with obesity. The resubmission noted that, given the comprehensively revised patient population, place in therapy, clinical claim and economic evaluation, it is best viewed as a *de novo* application for the recently approved TGA indication for secondary prevention of cardiovascular events, rather than a continuation of previous listing requests for use in patients with overweight and obesity.

1.2 The resubmission identified three alternative target patient populations with established cardiovascular disease based on different Body Mass Index (BMI) thresholds: ≥27 kg/m^2, ≥35 kg/m^2 and ≥40 kg/m^2. The resubmission stated that the patient population with a BMI ≥40 kg/m^2 should be considered the main population as these patients represent a priority population with the highest clinical need. The resubmission claimed that these patient populations remain at significant risk of further cardiovascular events despite standard of care therapies and there is a clinical need for semaglutide as a weight loss treatment with proven reductions in cardiovascular events.

1.3 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	Adults with established cardiovascular disease (defined as a documented history of prior myocardial infarction, stroke, or symptomatic peripheral arterial disease) and: - Option 1 (priority population): with BMI ≥40 kg/m^2 or ≥37.5 kg/m^2 for Aboriginal and Torres Strait Islander/Asian persons - Option 2: with BMI ≥35 kg/m^2 or ≥32.5 kg/m^2 for Aboriginal and Torres Strait Islander/Asian persons - Option 3: with BMI ≥27 kg/m^2 or ≥25 kg/m^2 for Aboriginal and Torres Strait Islander/Asian persons
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. Patients who are unable to titrate to the recommended maintenance dose of 2.4 mg can decrease to a maintenance dose of 1.7 mg. This treatment regimen is intended to be used strictly in addition to individually tailored, clinically appropriate standard of care for initial management and secondary prevention of cardiovascular disease in an overweight or obese patient population, including any and all recommended and publicly funded, or otherwise reasonably accessible and affordable pharmacological, surgical, clinical, and/or lifestyle based interventions used within this to ensure maximal and sustained benefits of treatment.
Comparator	Placebo in combination with standard of care therapies
Outcomes	Reduction in weight, improvement in cardiometabolic risk factors, reduced incidence of downstream complications (cardiovascular events, diabetes, chronic kidney disease), increased survival and improved quality of life.
Clinical claim	Semaglutide is superior in terms of efficacy and inferior in terms of safety compared to placebo

Source: Table 1-3, p23 of the resubmission
Abbreviations: BMI, body mass index
Note: The resubmission proposed adjustments to the qualifying BMI thresholds (-2.5 kg/m^2) for Aboriginal and Torres Strait Islanders as well as patients of Asian descent.

2 Background

Registration status

2.1 Semaglutide (Wegovy®, 0.25, 0.5, 1.0, 1.7 and 2.4 mg single or multi dose pen) is TGA registered for the following indications:

- As an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease, with a BMI ≥27kg/m^2, and without established Type 1 or Type 2 diabetes.
- 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/m^2 (obesity), or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.
- As an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with initial obesity (based on CDC growth charts) and body weight above 60 kg. Treatment should be re-evaluated and discontinued if adolescent patients have not reduced their BMI by at least 5% after 12 weeks on the 2.4 mg or maximum tolerated dose.

2.2 The TGA approved product information for semaglutide (Wegovy®) includes a Black Triangle symbol to signify it is subject to additional monitoring in Australia as part of the TGA Black Triangle Scheme. The Black Triangle is a visual reminder to encourage health practitioners and patients to report a problem or side effect.

2.3 Semaglutide (Ozempic®, 0.25, 0.5, 1.0 mg multi dose pen) 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

2.4 The sponsor presented a Category 2 submission to the March 2022 PBAC meeting requesting a Section 85 (General Schedule) PBS listing for semaglutide for the treatment of severe obesity (BMI ≥35 kg/m^2 with a least one weight-related comorbidity).

2.5 The PBAC did not recommend semaglutide for the requested 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 Public Summary Document [PSD], March 2022 PBAC meeting).

2.6 In November 2023, the sponsor presented a standard re-entry submission requesting a General Schedule Authority Required (telephone/online) listing for semaglutide for the treatment of severe obesity (with BMI ≥40 kg/m^2 and multiple weight-related comorbidities) after prior participation in an appropriate lifestyle-based weight management intervention.

2.7 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. The PBAC considered that information from the SELECT cardiovascular outcomes trial 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 (para 7.1 semaglutide PSD, November 2023 PBAC meeting).

2.8 The PBAC considered semaglutide was not cost effective at the price proposed. 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 (para 7.1 semaglutide PSD, November 2023 PBAC meeting).

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	№.of Rpts	Available brands
SEMAGLUTIDE						
INITIAL TREATMENT						
Semaglutide, pre-filled single dose pen, 0.25 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	0	Wegovy
Semaglutide, pre-filled single dose pen, 0.5 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	0	
Semaglutide, pre-filled single dose pen, 1.0 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	0	
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	0	
CONTINUING TREATMENT						
Semaglutide, pre-filled single dose pen, 1.7 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	5	Wegovy
Semaglutide, pre-filled single dose pen, 2.4 mg in 0.5 mL	$[redacted] (published) $[redacted] (effective)	$[redacted] (published) $[redacted] (effective)	1	4	5	
Category / Program: General Schedule						
Prescriber type: ☒Medical Practitioners						
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)						
Indication: Established cardiovascular disease						
Treatment Phase: Initial treatment						
Clinical criteria:						
Patient must have a confirmed diagnosis of prior myocardial infarction or stroke, or symptomatic peripheral arterial disease; AND						
AND						
Clinical criteria (Option 1):						
Patient must have a Body Mass Index greater than or equal to 40 kg/m^2, or 37.5 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people						
Clinical criteria (Option 2):						
Patient must have a Body Mass Index greater than or equal to 35 kg/m^2, or 32.5 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people						
Clinical criteria (Option 3):						
Patient must have a Body Mass Index greater than or equal to 27 kg/m^2, or 25 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people						
Treatment criteria:						
Patient must not receive more than 16 weeks of treatment under this restriction						
The treatment must be used in conjunction with standard of care associated with the management of cardiovascular disease and prevention of future cardiovascular events						
Population criteria:						
Patient must be aged 18 years or older						
Administrative Advice:						

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
No increase in the maximum quantity or number of units may be authorised
No increase in the maximum number of repeats may be authorised
Special Pricing Arrangements apply
Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Indication: Established cardiovascular disease
Treatment Phase: Grandfathering arrangement
Clinical criteria:
Patient must have had at the time of initiating non-PBS subsidised treatment with this drug for this condition: A confirmed diagnosis of prior myocardial infarction or stroke, or symptomatic peripheral arterial disease
AND
Clinical criteria (Option 1):
Patient must have a Body Mass Index greater than or equal to 40 kg/m^2, or 37.5 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people
Clinical criteria (Option 2):
Patient must have a Body Mass Index greater than or equal to 35 kg/m^2, or 32.5 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people
Clinical criteria (Option 3):
Patient must have a Body Mass Index greater than or equal to 27 kg/m^2, or 25 kg/m^2 for Aboriginal or Torres Strait Islander or Asian people
Treatment criteria:
Patient must not receive more than 16 weeks of treatment under this restriction
The treatment must be used in conjunction with standard of care associated with the management of cardiovascular disease and prevention of future cardiovascular events
Population criteria:
Patient must be aged 18 years or older
Administrative Advice:
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
No increase in the maximum quantity or number of units may be authorised
No increase in the maximum number of repeats may be authorised
Special Pricing Arrangements apply
Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Indication: Established cardiovascular disease
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
Treatment criteria:
The treatment must be used in conjunction with standard of care associated with the management of cardiovascular disease and prevention of future cardiovascular events
Population criteria:
Patient must be aged 18 years or older
Administrative Advice:

The measured weight and height of the patient at the time STREAMLINED Authority is requested must be included in the medical record
No increase in the maximum quantity or number of units may be authorised
No increase in the maximum number of repeats may be authorised
Special Pricing Arrangements apply

3.1 The current resubmission proposed a special pricing arrangement with lower effective DPMQs for the lower dose strengths (0.25, 0.5, 1.0 mg; $[redacted] versus $[redacted]) and the 1.7 mg dose strength ($[redacted] versus $[redacted]) but a higher effective DPMQ for the 2.4 mg dose strength ($[redacted] versus $[redacted]) compared to the November 2023 submission. The proposed prices for the lower dose strengths are higher than the current prices for these dose strengths under the existing listing for type 2 diabetes.

3.2 The proposed essential elements did not have sufficient repeats for the lower dose strengths (0.25, 0.5 and 1.0 mg) to be used for maintenance dosing or patients requiring slower dose escalation. While this was consistent with the recommended dosing regimen in the product information, it was inconsistent with the clinical evidence from the key trial, economic analysis and budget impact model all of which included a small proportion of patients using the lower dose strengths as maintenance therapy. The Pre-Sub-Committee Response (PSCR) argued that the number of repeats was intended to provide a real-world reflection of the trial-based incentive for patients and prescribers to follow the recommended titration schedule. The ESC advised that adverse events may increase the duration of titration and considered it would be reasonable to allow a repeat for initial treatment for those who may need to titrate more slowly. In addition, noting that 16.23% of patients in the SELECT trial used lower dose strengths as maintenance, the ESC considered it may be reasonable to allow lower doses for continuing treatment. The pre-PBAC response acknowledged that the product information allows delaying dose escalation in cases of significant gastrointestinal symptoms.

3.3 The resubmission proposed three alternative patient populations with atherosclerotic cardiovascular disease using different BMI thresholds as a qualifying criterion: ≥40 kg/m^2 (Option 1), ≥35 kg/m^2 (Option 2) and ≥27 kg/m^2 (Option 3) with specific adjustments for people of Asian or Aboriginal or Torres Strait Islander ethnicity. Overall, the evaluation noted that Option 3 most closely aligns with the clinical trial evidence and the TGA approved restrictions for established cardiovascular disease and weight loss. The ESC considered that if the purpose of treatment was secondary prevention for all people with eCVD, then the ITT population (patients with BMI ≥27 kg/m^2) was appropriate. If the purpose of treatment was to target secondary prevention of CVD in patients with obesity, then option 1 or 2 would be appropriate, as patients with a BMI ≥40 kg/m^2 or 35 kg/m^2 are very likely to have excess adiposity. However, the ESC also noted the recent publication in The Lancet Diabetes &

Endocrinology[1] in which the definition and diagnostic criteria of clinical obesity was moving away from solely relying on BMI, and there was a consensus statement regarding diagnostic criteria for clinical obesity in adults with respect to CVD. The ESC considered criteria beyond BMI may also need to be considered.

3.4 The resubmission proposed an Authority Required (telephone/online) listing for the initial and grandfathered listings and a Streamlined Authority for the continuation listing. The evaluation noted this is consistent with the current PBS listing of semaglutide for type 2 diabetes. However, a recent DUSC analysis of semaglutide for type 2 diabetes suggested 73% of treatment initiations were outside of the target PBS population and 56% of patients appeared to be initiated using the Streamlined Authority continuation listing rather than the Authority Required (telephone/online) initial listing.

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

4 Population and disease

4.1 Cardiovascular disease is a broad term used to describe a variety of conditions that affect the heart and blood vessels including myocardial infarction ("heart attack"), stroke, angina, transient ischaemic attack ("mini-stroke"), peripheral arterial disease, heart failure/cardiomyopathy, atrial fibrillation, rheumatic heart disease and congenital heart disease (AIHW Heart, stroke and vascular disease report 2024). There are multiple established and interrelated risk factors for cardiovascular disease including hypercholesterolaemia, hypertension, diabetes, chronic kidney disease, physical inactivity, poor diet, smoking, excess alcohol consumption, overweight and obesity, family history (genetics) and/or ethnicity (NHS 2025). In Australia it was estimated that 1.3 million adults (6.7%) were living with cardiovascular disease in 2022 with a higher incidence in males (7.6%) versus females (5.8%) and an increasing incidence with age (28% of individuals aged ≥75 years) (ABS National Health Survey 2022). Cardiovascular disease is associated with both increased mortality and lower quality of life.

4.2 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

[1] Rubino, F. et al; "Definition and diagnostic criteria of clinical obesity", *The Lancet Diabetes & Endocrinology*, Volume 13, Issue 3, 2025, Pages 221-262

flavoured drinks), the availability of convenience foods, the built environment etc. Obesity is a highly prevalent disease which has been steadily increasing over time in the Australian population, with the latest estimate indicating that approximately 1 in 3 adults are obese (ABS National Health Survey 2017-2018).

4.3 Obesity is typically classified based on body mass index (ratio of weight to height) and/or waist circumference using the following thresholds (noting different thresholds are used for some population groups):

- BMI between 18.5 and 24.9 kg/m^2 is considered healthy for adults.
- BMI between 25 and 29.9 kg/m^2 is considered overweight for adults.
- BMI between 30 and 34.9 kg/m^2 is considered obese for adults.
- BMI of 35 kg/m^2 and above is considered severely obese for adults.
- In men a waist circumference of 94 centimetres or more indicates an increased risk of weight-related comorbidities and a measurement of 102 centimetres or more indicates a greatly increased risk of weight-related comorbidities.
- In women a waist circumference of 80 centimetres or more indicates an increased risk of weight-related comorbidities and a measurement of 88 centimetres or more indicates a greatly increased risk of weight-related comorbidities.

4.4 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, and some cancers. Patients with obesity often also 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).

4.5 The resubmission targeted a subgroup of adult patients with a prior history of specific cardiovascular events (myocardial infarction, stroke and peripheral arterial disease) who were either overweight or obese. This population was well-defined and broadly consistent with the key clinical trial data.

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

5 Comparator

5.1 The resubmission nominated placebo as the main comparator as a proxy for standard of care management in patients with established cardiovascular disease. The main argument in support of this nomination was the claim that semaglutide will be used as an add-on to standard of care therapies. The ESC agreed with the evaluation that this was reasonable.

5.2 The resubmission argued that tirzepatide (a dual GLP-1/GIP therapy) should not be considered a near market comparator on the basis that its key cardiovascular outcome trial is still underway (SURMOUNT-MMO, estimated study completion: October 2027) and tirzepatide does not have a specific TGA indication for patients with established cardiovascular disease. The ESC agreed with the evaluation that exclusion of

tirzepatide as a near market comparator may not be reasonable, given that tirzepatide is currently TGA approved as 'an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of: ≥30 kg/m^2 (obesity) or ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes or type 2 diabetes mellitus)' which is inclusive of the target population in the current resubmission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (89), health care professionals (18) and health care-related organisations (10) and consumer groups (5) via the Office of Health Technology Assessment Consultation Hub. The PBAC noted that of the 80 individuals that provided inputs saying they had used the medicine, many focused on a broader PBS listing for weight loss, and they did not indicate they specifically have eCVD with obesity as defined in the submission. However, a number did discuss having obesity with heart disease and/or high blood pressure and of those many noted positive effects on their heart health and blood pressure. They also described the benefits associated with the weight loss they experienced on their overall health, noting that it has helped them manage pain, increase mobility and enhanced psychological wellbeing as well as reducing the need for blood pressure medication for some. They reported improved quality of life and some of the inputs emphasised the importance of having access to GLP-1 medicines as a complementary tool in achieving and maintaining a healthy weight, which has supported their ability to adhere with other cardiac health improving interventions such as exercise and dietary changes. The input from individuals highlighted the financial and health equity pressures associated with cost and gaining access to semaglutide. The PBAC noted that the input received from individuals that focused on a broader PBS listing of semaglutide for weight loss would be included in work being undertaken by the Department to support the PBAC in providing its response to a March 2025 request from the Minister for Health, Disability and Ageing on equitable access to

pharmacotherapies to treat obesity.[2]

6.3 The PBAC noted input from health care professionals emphasised that many patients with eCVD have concurrent obesity, which is a known risk modifier for future adverse CVD events and treatment complications. The input emphasised the clinical findings of the SELECT trial on cardiovascular-related outcomes and the important implications of the trial outcomes on future clinical practice as it relates to treatment of eCVD and obesity. Health care professional input described people often blaming themselves for their obesity which was reported to enshrine stigma and a sense of shame that can cause people to disengage with the health system. The PBAC acknowledged health care professional feedback that BMI eligibility criteria should be carefully considered in certain subpopulations that may be more vulnerable or at risk of cardiovascular events, particularly Aboriginal or Torres Strait Islander peoples. Health care professional input noted that current access to semaglutide is limited by its high cost, creating equity issues for those from lower socioeconomic backgrounds and in rural and remote areas where prices may be further elevated.

6.4 Consumer groups were supportive of the proposal to provide subsidised access to semaglutide, though the majority of groups focussed on the obesity and weight management benefits of the medicine. Health Consumer Council WA and Weight Issues Network described the stigma associated with accessing medical support for people who live in larger bodies. The PBAC noted input from the Hearts4Heart, the Obesity Collective and Heart Support Australia regarding the importance of GLP-1 medicine access as a complementary intervention to limit progression of CVD in patients (particularly where access to allied healthcare interventions such as dietitians may be limited), and the use of semaglutide to support sustained uptake of other important healthcare interventions supporting cardiac health (including exercise and dietary modifications).

6.5 The PBAC noted the input from ASMANT Aboriginal Corporation and National Aboriginal Community Controlled Health Organisation (NACCHO) regarding the important equity implications of supporting access to semaglutide for Aboriginal and Torres Strait Islander peoples. The input noted that cardiovascular disease is a major driver of premature mortality in Aboriginal people. The input also emphasised that adjustments to eligibility criteria such as the BMI threshold be considered, to include risk calculators that include indigeneity and socio-economic status, given the disproportionate health effects of eCVD and obesity in this population and the significant existing structural barriers to accessing existing treatments that would

[2] House of Representatives. (2025). Responses: Obesity. Parliament of Australia. https://www.aph.gov.au/Parliamentary_Business/Hansard/Hansard_Display?bid=chamber/hansardr/28774/&sid=0147#:~:text=Mr%20Dreyfus%20KC-,Obesity,-Dear%20Chair

improve cardiovascular and obesity outcomes.

6.6 The PBAC noted input from the RACGP regarding the limited progress on reducing obesity in the population despite Government endorsement of the National Obesity Strategy 2022-2032. The RACGP input advised that the treatment landscape had changed since the release of the National Obesity Strategy with the availability of GLP-1 medicines. The PBAC noted the RACGP suggested prioritisation of individuals with BMI ≥ 40 kg/m^2 (or ≥ 35 kg/m^2 for Aboriginal and Torres Strait Islander peoples with adjustments for other specific populations) who had additional obesity-related health impairments.

6.7 The PBAC noted advice from the Australian and New Zealand Society for Vascular Surgery, suggesting the use of GLP-1 receptor agonists be embedded within multidisciplinary models of care, including vascular surgical services, to maximise health benefits. The PBAC noted advice from Impact Obesity, which emphasised the importance of weight loss for patients with eCVD to meet recommended lifestyle and exercise requirements. The PBAC also noted input from iNova pharmaceuticals regarding concerns about the high possibility of off-label prescribing and the potential cost implications for the PBS of such use.

Clinical trials

6.8 The resubmission was based on one head-to-head randomised trial comparing cardiovascular outcomes with semaglutide to placebo in patients with established cardiovascular disease who were obese or overweight (SELECT). The resubmission also provided additional *post hoc* analyses of the SELECT trial based on subgroups with BMI ≥35 kg/m^2 and ≥40 kg/m^2.

6.9 Details of the key trial presented in the resubmission are provided in Table 2.

Table 2: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
NNC0113-0217 (SELECT)	Novo Nordisk (2023). Semaglutide effects on cardiovascular outcomes in people with overweight or obesity.	Internal study report
	Lincoff et al (2023). Semaglutide and cardiovascular outcomes in obesity without diabetes.	*New England Journal of Medicine* 389:2221-2232
	Ryan et al (2024). Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial.	*Nature Medicine* 30:2049-2057
	Colhoun et al (2024). Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial.	*Nature Medicine* 30:2058-2066
	Kahn et al (2024). Effect of semaglutide on regression and progression of glycemia in people with overweight or obesity but without diabetes in the SELECT trial.	*Diabetes Care* 47(8):1350-1359
	Lingvay et al (2024). Semaglutide and cardiovascular outcomes by baseline HbA1c and change in HbA1c in people with overweight or obesity but without diabetes in SELECT.	*Diabetes Care* 47:1360-1369

Source: Table 2-3, p52 of the resubmission

6.10 The key features of the SELECT trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Semaglutide versus placebo						
SELECT	17,604	MC, R, DB, PC (event-driven trial duration, mean 40 months)	Low	Established cardiovascular disease and BMI ≥27 kg/m^2	Cardiovascular events, mortality, change in BMI and other biomarkers, quality of life, adverse events	Baseline characteristics and estimated treatment effects

Source: Section 2.3.2.1, p55; Section 2.4, pp58-68 of the resubmission and the SELECT trial report
Abbreviations: BMI, body mass index; DB, double blind; MC, multi-centre; PC, placebo-controlled; R, randomised

6.11 The SELECT trial specifically excluded patients with pre-existing diabetes. However, the mean HbA1c level was 5.8% and the majority of patients met the HbA1c criterion for prediabetes (66% based on HbA1c of 5.7 to 6.4%). The resubmission acknowledged that the trial excluded patients with pre-existing diabetes but noted the SUSTAIN-6 cardiovascular outcomes trial of semaglutide (Ozempic®, 0.25, 0.5, 1.0 mg multi dose pen) supports the use of semaglutide in type 2 diabetes patients with high cardiovascular risk.

6.12 The evaluation considered it was unclear whether the circumstances of use from the SELECT trial would be representative of Australian clinical practice. Real-world utilisation data from international observational studies suggested much higher discontinuation rates (approximately 50% within the first year), with slower titration schedules and lower maintenance doses, with only 10% of patients following treatment guidelines of increasing the dose every 4 weeks (Gasoyan 2025, Mayer 2024, Ladebo 2024). Among Danish patients who received at least 10 prescriptions of semaglutide, more than half were on maintenance doses (1.7 mg: 29%, 2.4 mg: 26%) and the rest were on lower doses (0.25 mg: 1%, 0.5 mg: 5%, 1 mg: 33%) or had stopped treatment at that point (6%) (Ladebo 2024). However, the studies acknowledged that semaglutide supply issues and the dynamics of private markets may have also impacted these estimates. The PSCR noted that, compared to the observational studies referenced, the proposed PBS population were at high risk of secondary cardiovascular events and argued that they are likely to be more motivated and inclined towards optimal titration and persistence. The ESC advised that, even with supply and cost issues addressed, adverse events were likely to be a key contributor to slower titration or lower maintenance doses rather than motivation. The ESC disagreed with the suggestion that patients without eCVD are opting for maintenance at lower doses or discontinuation due to lack of motivation.

6.13 The resubmission noted that semaglutide and placebo were used in combination with 'optimised' background therapy for cardiovascular risk factors as well as lifestyle counselling (every 4 weeks during titration and then every 3 months during maintenance) in the SELECT trial. The generalisability of background therapy in the trial to Australian clinical practice is uncertain, as while SELECT was optimised for cardiovascular risk management, there was limited use of PCSK9 inhibitors, SGLT2 inhibitors and icosapent ethyl, all of which are PBS-listed for established cardiovascular disease. The resubmission did not provide any further detail on lifestyle

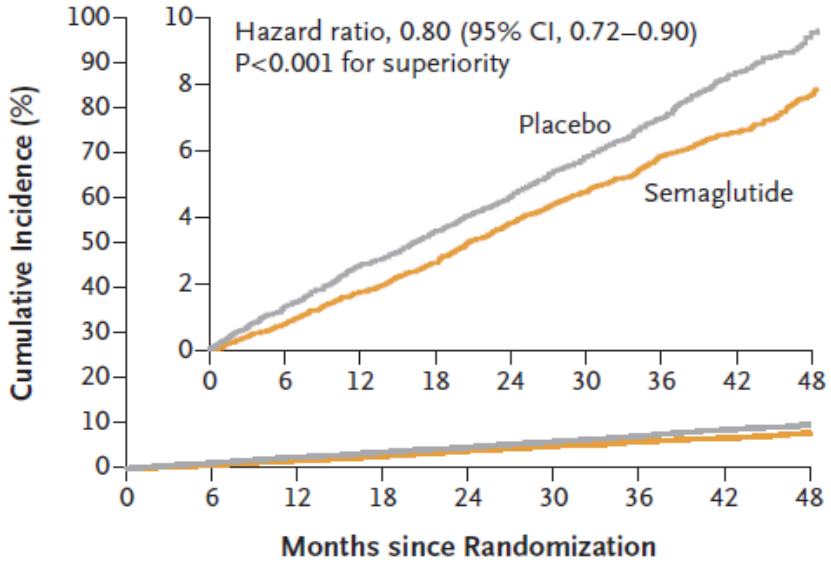
counselling provided during the key trial and it was unclear whether this would be representative of Australian clinical practice. The PSCR acknowledged that standard of care for secondary prevention of CVD has improved since the SELECT trial was initiated. The PSCR argued that the types of cardiovascular-related medicines ongoing at randomisation were similar between treatment groups and noted that the proportion of subjects initiating any type of cardiovascular-related medication during the trial was slightly lower with semaglutide compared to placebo.

6.14 The use of GLP-1 analogues was not permitted in patients who developed diabetes in the SELECT trial. This was not consistent with Australian clinical practice.

Comparative effectiveness

6.15 The primary outcome of the SELECT trial was the time to first major adverse cardiovascular event (composite endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) and is shown in Figure 1.

Figure 1: Time to first MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) (ITT)



No. at Risk									
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

Source: Figure 1, Lincoff 2023 publication
Abbreviations: CI, confidence interval; ITT, intention to treat; MACE, major adverse cardiovascular event
Note: The inset graph shows the same data on an enlarged y axis

6.16 Treatment with semaglutide was associated with a statistically significant decreased risk of cardiovascular events compared to placebo (HR 0.80, 95% CI 0.72, 0.90). The difference was primarily driven by non-fatal myocardial infarction events. Sensitivity analyses using alternative methods for handling of missing data produced results that were consistent with the primary analysis.

6.17 Supportive analyses were conducted using alternative MACE definitions. Results for semaglutide versus placebo based on time to first event of all-cause death, non-fatal myocardial infarction or non-fatal stroke (HR 0.80, 95% CI 0.72, 0.88); expanded MACE

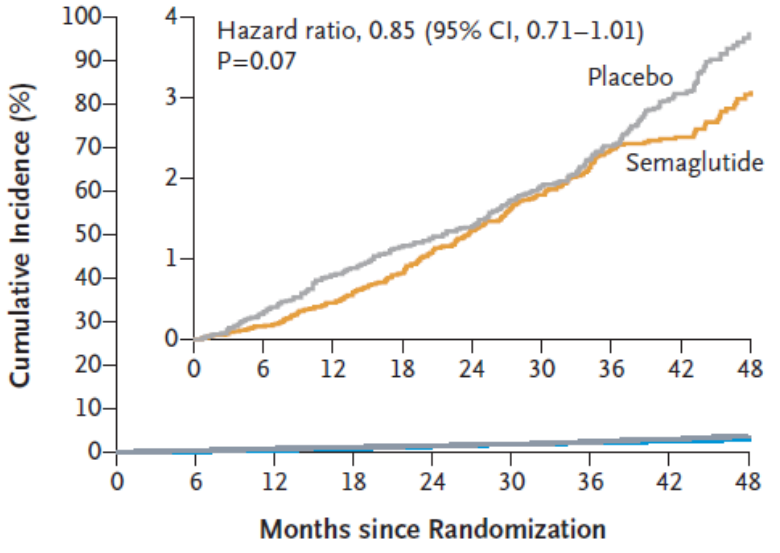
consisting of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation (HR 0.80, 95% CI 0.73, 0.87); and expanded MACE including all-cause death (HR 0.80, 95% CI 0.73, 0.87) were consistent with results for the primary analysis.

6.18 The resubmission also identified several pre-specified mediation analyses based on SELECT trial data that investigated possible interactions between changes in cardiovascular risk factors (including body weight) and the incidence of MACE (Deanfield 2024; Colhoun 2024; Plutzky 2025). The ESC noted that only the Deanfield 2024 study was available as a full paper (with Colhoun 2024 and Plutzky 2025 available in abstract or poster form only) and that the confidence intervals for a number of variables analysed went below 0% or exceeded 100%, which suggested the analyses may be unstable and should be interpreted with caution. Overall, the analyses suggest that cardiovascular benefits associated with semaglutide could only be partially attributed to weight loss and glycaemic reductions. The SELECT study investigators indicated that the underlying mechanisms for cardiovascular benefit require further investigation. The ESC noted that, while further investigation was required, the economic model assumed an additional increased risk of cardiovascular events based on BMI, with risk multipliers based on this assumption being a key driver of the models (see Table 10). The ESC noted that the PSCR suggested that the SELECT trial was not necessarily powered to detect increasing cardiovascular risk with increasing BMI and hence the external BMI multipliers were included in the model to reflect the higher clinical need and greater capacity to benefit in the higher BMI subgroups. The ESC considered that, even if the trial was underpowered, an increase in the baseline risk in the higher BMI groups would be expected; however this was not always the case in the SELECT trial, e.g. coronary revascularisation procedures in the placebo arm were higher with lower BMI (see Table 8). The ESC considered it may be more reasonable to conclude that, given the multiple possible interactions between changes in cardiovascular risk factors and the incidence of MACE, the mechanisms for cardiovascular benefit from semaglutide treatment require further investigation, rather than that they were undervalued in the SELECT trial outcomes. Risk multipliers are a blunt tool to apply in this situation, and the ESC considered it was inappropriate to adjust the baseline risk of the trial population by the risk of developing CVD, diabetes or CKD based on BMI from external sources.

6.19 Results from pre-specified subgroup analyses for sex, age and BMI appeared consistent with the primary analysis.

6.20 The time to cardiovascular death (including undetermined cause of death) was the first confirmatory secondary endpoint assessed in the SELECT trial using a hierarchical testing structure (shown in Figure 2).

Figure 2: Time to cardiovascular death (ITT)



Source: Figure 1, Lincoff 2023 publication
Abbreviations: CI, confidence interval; ITT, intention to treat
Note: The inset graph shows the same data on an enlarged y axis

6.21 Death from cardiovascular causes occurred in 2.5% of patients in the semaglutide arm and 3.0% of patients in the placebo arm. However, the results failed superiority testing as they did not achieve statistical significance (HR 0.85, 95% CI 0.71, 1.01). Superiority testing was not performed for remaining secondary endpoints in the hierarchy: heart failure composite including cardiovascular death or hospitalisation/ urgent medical visit for heart failure (HR 0.82, 95% CI 0.71, 0.96) and all-cause death (HR 0.81, 95% CI 0.71, 0.93).

6.22 Time to event analyses for individual cardiovascular events are summarised in Table 4.

Table 4: Key cardiovascular secondary outcomes, time to first event analyses (ITT)

Outcome	Semaglutide N = 8,803	Placebo N = 8,801	Hazard ratio (95% CI)
Time to cardiovascular death [a]	223 (2.5%)	262 (3.0%)	0.85 (0.71, 1.01)
Time to all-cause death	375 (4.3%)	458 (5.2%)	0.81 (0.71, 0.93)
Time to first non-fatal myocardial infarction	234 (2.7%)	322 (3.7%)	0.72 (0.61, 0.85)
Time to first non-fatal stroke	154 (1.7%)	165 (1.9%)	0.93 (0.74, 1.15)
Time to first coronary revascularisation	473 (5.4%)	608 (6.9%)	0.77 (0.68, 0.87)
Time to first unstable angina requiring hospitalisation	109 (1.2%)	124 (1.4%)	0.87 (0.67, 1.13)
Time to first heart failure event [b]	97 (1.1%)	122 (1.4%)	0.79 (0.60, 1.03)

Source: Table 14.2.63, p669; Table 14.2.64, p670; Table 14.2.69, p676; Table 14.2.70, p677; Table 14.2.75, p682; Table 14.2.76, p683; Table 14.2.78, p685; Table 14.2.79, p686; Table 14.2.81, p688; Table 14.2.82, p689 of the SELECT trial report
Abbreviations: CI, confidence interval; ITT, intention to treat
[a] Includes undetermined cause of death
[b] Includes heart failure hospitalisation and urgent heart failure medical visit
Note: Treatment effect estimates for supportive secondary endpoints were unadjusted for multiplicity

6.23 Time to first event analyses of secondary end points indicate that semaglutide was associated with a decreased risk of all-cause death, non-fatal myocardial infarction and coronary revascularisation compared to placebo. There was no apparent difference in cardiovascular death, non-fatal stroke, unstable angina requiring hospitalisation and heart failure requiring hospitalisation/urgent care between treatment arms.

6.24 Compared to the whole trial population, subgroups with BMI of ≥35 and ≥40 kg/m^2 were associated with numerically increased rates of cardiovascular death, non-fatal stroke and heart failure hospitalisations, numerically decreased rates of coronary revascularisation and unstable angina requiring hospitalisation and similar rates of non-cardiovascular death and non-fatal myocardial infarction.

6.25 The time to first occurrence of HbA1c ≥6.5% is summarised in Table 5.

Table 5: Time to first occurrence of HbA1c ≥6.5% (ITT)

Outcome	Semaglutide (N = 8,803)	Placebo (N = 8,801)	Hazard ratio (95% CI)
Patients, n (%)	306 (3.5)	1,059 (12.0)	0.27 (0.24, 0.31)

Source: Table 14.2.99 and Table 14.2.100, pp708-709 of the SELECT trial report
Abbreviations: CI, confidence interval; ITT, intention to treat

6.26 Treatment with semaglutide was associated with a reduced risk of having an HbA1c ≥6.5% compared to placebo.

6.27 Results from *post hoc* subgroup analyses suggested that baseline HbA1c levels may be a treatment effect modifier, with a potentially smaller magnitude of benefit in the subgroup with HbA1c less than 5.7%. Results based on other subgroups were generally consistent with the primary analysis.

6.28 The mean change in body weight over time is summarised in Table 6.

Table 6: Change in body weight from baseline to Week 104 (ITT)

	Semaglutide (N = 8,803)			Placebo (N = 8,801)			Treatment difference (95% CI)
	Baseline	Week 104	Mean % change (SE)	Baseline	Week 104	Mean % change (SE)	
Weight, kg, mean (SD)	96.5 (17.5)	87.4 (17.7)	-9.4% (0.1)	96.8 (17.8)	95.5 (18.0)	-0.9 % (0.1)	-8.5% (-8.8, -8.3)

Source: Table 2-18, p77 of the resubmission; Table 14.2.108, p717 of the SELECT trial report
Abbreviations: CI, confidence interval; ITT, intention to treat; SD, standard deviation; SE, standard error

6.29 Treatment with semaglutide was associated with a reduction in body weight over time compared to placebo. Mean body weight decreased from baseline through to Week 65 with semaglutide, after which a plateau was reached and sustained for the remainder of the trial. With placebo, mean body weight appeared relatively stable throughout the trial.

6.30 Results from *post hoc* subgroup analyses suggested that baseline age, sex, BMI category, region, race and waist-to-height ratio may all be treatment effect modifiers for weight change. The most notable difference was the estimated treatment difference in females (-11.11%; 95% CI -11.56, -10.66) compared to males (-7.50%; 95% CI -7.78, -7.23).

6.31 Treatment with semaglutide was associated with a decreased risk of events related to a deterioration in kidney function compared to placebo. The treatment effect was

mainly driven by the onset of persistent macroalbuminuria, with few occurrences of other events. There was a slight decline from baseline in estimated glomerular filtration rate (eGFR) in both treatment groups over the trial duration. At 104 weeks, treatment with semaglutide was associated with a numerically smaller decline in eGFR compared to placebo (semaglutide -0.84, placebo -1.65; difference of 0.81 mL/min/1.73 m^2).

6.32 Results from *post hoc* subgroup analyses of change in eGFR suggested that baseline age, eGFR and BMI category may be treatment effect modifiers. In particular, there was no statistically significant difference in eGFR decline for patients with early-stage disease but there were nominally significant improvements in eGFR for patients with more advanced disease. Patients with more advanced disease in both treatment arms typically demonstrated stabilisation or improvement in eGFR scores over time.

6.33 Treatment with semaglutide was associated with small improvements in EQ-5D-5L index (treatment difference: 0.01; 95% CI 0.01, 0.02) and visual analogue scores (treatment difference 1.60; 95% CI 1.16, 2.04) compared to placebo.

6.34 Compared to the whole trial population, patients in higher BMI categories had lower baseline EQ-5D-5L index scores. There was a statistically significant interaction between subgroups based on the BMI threshold of 35 kg/m^2 and a borderline statistically significant interaction based on the 40 kg/m^2 threshold. Results for these *post hoc* subgroups were similar to those in the ITT population, showing that semaglutide was associated with small improvements in EQ-5D-5L index scores compared to placebo.

Comparative harms

6.35 The SELECT trial collected data for all serious adverse events and selected pre-defined categories of adverse events (regardless of seriousness) such as adverse events leading to treatment discontinuation, COVID-19 related adverse events and other safety focus areas. Both the resubmission and TGA delegate noted that it would be difficult to identify new safety concerns (other than serious adverse events) given the non-systematic approach in the trial. Adverse events that were not serious or did not fall in any of the pre-defined adverse event categories would not necessarily be captured. However, the resubmission claimed that safety findings in the trial were consistent with data from the larger safety database which includes other semaglutide clinical trial programs and post-market surveillance.

6.36 An overall summary of the adverse events reported in the SELECT trial is presented in Table 7.

Table 7: Summary of adverse events in the SELECT trial

	Semaglutide (N = 8,803)		Placebo (N = 8,801)	
	Incidence, n (%)	Events, n (rate/100 pt-yrs)	Incidence, n (%)	Events, n (rate/100 pt-yrs)
Serious adverse events				
Serious events	2,941 (33.4)	6,622 (22.6)	3204 (36.4)	7,507 (25.8)
- Cardiac disorders	1,008 (11.5)	1,414 (4.8)	1,184 (13.5)	1,800 (6.2)
- Infections and infestations	624 (7.1)	805 (2.8)	738 (8.4)	937 (3.2)
- Nervous system disorders	444 (5.0)	544 (1.9)	496 (5.6)	623 (2.1)
- Surgical and medical procedures	433 (4.9)	516 (1.8)	548 (6.2)	675 (2.3)
- Neoplasms benign, malignant, unspecified	405 (4.6)	478 (1.6)	402 (4.6)	462 (1.6)
- Gastrointestinal disorders	342 (3.9)	455 (1.6)	323 (3.7)	403 (1.4)
Serious events that were fatal [a]	371 (4.2)	480 (1.6)	460 (5.2)	595 (2.0)
Adverse events leading to trial product discontinuation (including non-serious events)				
Permanent treatment discontinuation	1,461 (16.6)	2,073 (7.1)	718 (8.2)	907 (3.1)
- Gastrointestinal disorders	880 (10.0)	1,195 (4.1)	172 (2.0)	200 (0.7)
- Nervous system disorders	124 (1.4)	128 (0.4)	92 (1.0)	101 (0.4)
- Metabolism and nutrition disorders	108 (1.2)	111 (0.4)	27 (0.3)	29 (0.1)
- General disorders and administration site	105 (1.2)	106 (0.4)	47 (0.5)	47 (0.2)
Adverse events of special interest (including non-serious events)				
- COVID-19 related events	2,108 (23.9)	2,323 (8.9)	2,150 (24.4)	2,365 (9.1)
- Malignant neoplasms	422 (4.8)	517 (1.8)	418 (4.7)	505 (1.7)
- Gallbladder-related disorders	246 (2.8)	300 (1.0)	203 (2.3)	246 (0.9)
- Acute kidney failure	171 (1.9)	193 (0.7)	200 (2.3)	222 (0.8)
- Pancreatitis	29 (0.3)	33 (0.1)	30 (0.3)	33 (0.1)

Source: Table 2-26, p92 of the resubmission; Figure 12-1, p183, Figure 12-2, p184; Table 14.3.1.3, p864, Table 14.3.1.8, p933, Table 14.3.1.12, p980, Table 14.3.1.15, p1011, Table 14.3.1.20, p1029, Table 14.3.1.24, p1033, Table 14.3.1.29, p1039, Table 14.3.1.37, p1056, Table 14.3.1.45, p1068 of the trial report

Abbreviations: pt-yrs, patient-years

[a] Trial investigators could report more than one event with a fatal outcome for the same subject

6.37 Treatment with semaglutide was associated with a lower incidence of serious adverse events, including those that led to fatal outcomes, compared to placebo, primarily due to fewer serious cardiac disorder events. A slightly higher percentage of patients in the semaglutide arm experienced serious gastrointestinal disorders, of which the most frequently reported were inguinal hernia, diarrhoea and gastrointestinal haemorrhage.

6.38 A higher proportion of patients discontinued semaglutide compared to placebo due to adverse events, primarily due to the more frequent occurrence of gastrointestinal disorders such as nausea, diarrhoea and vomiting. Adverse events leading to treatment discontinuation were more frequent during the dose escalation phase but continued to occur throughout the trial period.

6.39 Treatment with semaglutide was also associated with more frequent gallbladder-related disorders, mainly driven by an imbalance in cholelithiasis.

6.40 The resubmission provided updated data on potential safety concerns with semaglutide based on a Periodic Benefit Risk Evaluation Report (June 2023 to May 2024). The report includes use of injectable (single dose and multi-dose pens) and oral semaglutide predominantly for type 2 diabetes and weight management.

6.41 During the reporting period, there were changes to the safety profile of semaglutide including the addition of intestinal obstruction as an important identified risk. In addition, there is an open and ongoing signal regarding cardioembolic stroke following the unblinding of clinical data from the FLOW study of semaglutide in patients with type 2 diabetes and chronic kidney disease.

6.42 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, acute pancreatitis and serious allergic reactions (injectable semaglutide for type 2 diabetes) and intestinal obstruction. Important potential risks include serious allergic reactions (oral semaglutide for type 2 diabetes and injectable semaglutide for weight management), 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.

6.43 The report acknowledged a high reporting rate of medication errors with semaglutide single-dose pens for weight management. The report stated that these errors were predominantly related to dosing errors (starting dose too high) and administration errors (insufficient pressure applied while using the device). The report noted higher starting doses may increase the risk of gastrointestinal events but otherwise concluded that the safety implications of these medication errors were limited.

Benefits/harms

6.44 A summary of comparative benefits and harms for semaglutide versus placebo based on the overall SELECT trial population (BMI ≥27 kg/m^2) and BMI subgroups (BMI ≥35 kg/m^2; ≥40 kg/m^2) is presented in Table 8.

Table 8: Comparative benefits and harms for semaglutide versus placebo in patients with established cardiovascular disease

Events per 1,000 patients treated for 3.5 years	Semaglutide	Placebo	Treatment difference
Overall population (patients with established cardiovascular disease and BMI ≥27 kg/m²)			
Cardiovascular death	28	32	-4
Non-cardiovascular death	18	25	-7
Non-fatal myocardial infarction	32	46	-14
Non-fatal stroke	21	21	0
Hospitalisation/urgent care for heart failure	18	21	-3
Hospitalisation for unstable angina	14	18	-3
Coronary revascularisation procedure	67	91	-24
Adverse events leading to treatment discontinuation[a]	249	109	+130
Patients with established cardiovascular disease and BMI ≥35 kg/m²			
Cardiovascular death	35	35	0
Non-cardiovascular death	21	25	-4
Non-fatal myocardial infarction	35	46	-11
Non-fatal stroke	25	25	0
Hospitalisation/urgent care for heart failure	25	32	-7
Hospitalisation for unstable angina	11	11	0
Coronary revascularisation procedure	67	84	-21
Adverse events leading to treatment discontinuation[a]	249	109	+130
Patients with established cardiovascular disease and BMI ≥40 kg/m²			
Cardiovascular death	35	39	-4
Non-cardiovascular death	28	28	0
Non-fatal myocardial infarction	28	42	-14
Non-fatal stroke	25	28	-3
Hospitalisation/urgent care for heart failure	21	28	-7
Hospitalisation for unstable angina	4	11	-7
Coronary revascularisation procedure	53	70	-17
Adverse events leading to treatment discontinuation[a]	249	109	+130

Source: Source: Table 1, Event rates report of the resubmission
Abbreviations: BMI, body mass index
[a] All treatment discontinuation estimates were based on the overall population of the SELECT trial

6.45 Based on the SELECT overall patient population (BMI ≥27 kg/m^2), for every 1,000 patients with established cardiovascular disease who were treated with semaglutide instead of placebo over 3.5 years there would be:

- 11 fewer deaths (primarily non-cardiovascular deaths).
- 44 fewer non-fatal cardiovascular events (primarily non-fatal myocardial infarction and coronary revascularisation procedures).
- 130 additional adverse events that result in treatment discontinuation (primarily gastrointestinal events).

6.46 Based on the SELECT subgroup population with BMI ≥35 kg/m^2, for every 1,000 patients with established cardiovascular disease who were treated with semaglutide instead of placebo over 3.5 years there would be:

- 4 fewer deaths (primarily non-cardiovascular deaths).
- 39 fewer non-fatal cardiovascular events (primarily non-fatal myocardial infarction and coronary revascularisation procedures).

- 130 additional adverse events that result in treatment discontinuation (primarily gastrointestinal events).

6.47 Based on the SELECT subgroup population with BMI ≥40 kg/m^2, for every 1,000 patients with established cardiovascular disease who were treated with semaglutide instead of placebo over 3.5 years there would be:

- 4 fewer deaths (primarily cardiovascular deaths).
- 48 fewer non-fatal cardiovascular events (primarily non-fatal myocardial infarction and coronary revascularisation procedures).
- 130 additional adverse events that result in treatment discontinuation (primarily gastrointestinal events).

Clinical claim

6.48 The resubmission described semaglutide as superior in terms of efficacy (in reducing major adverse cardiovascular events in patients with eCVD) and inferior in terms of safety compared to placebo. The ESC agreed with the evaluation that this claim was reasonable.

6.49 The following issues should be considered:

- The circumstances of use of semaglutide in the key trial may not be applicable to clinical practice. Real-world utilisation data suggest that patients undergo slower titration, remain on lower doses for maintenance and experience higher discontinuation rates compared to the trial. The evaluation considered these differences may lead to more modest treatment benefits than observed in the trial. The PSCR stated that the retrospective SCORE study (Smolderen 2025), using US claims data, suggested that semaglutide 2.4 mg may have larger treatment effects on cardiovascular events in clinical practice compared to the SELECT trial (3-point MACE endpoint; SCORE hazard ratio: 0.43, 95% CI 0.31, 0.61; SELECT hazard ratio 0.80, 95% CI 0.72, 0.90). The ESC considered this retrospective non-randomised study was less robust than the SELECT trial and its applicability to Australian clinical practice was unclear. The ESC agreed with the evaluation that differences in dosing and discontinuation rates may lead to more modest treatment benefits than observed in the trial.
- The generalisability of standard of care in the SELECT trial to Australian practice is uncertain given background therapy was optimised for cardiovascular risk management, but included limited use of PCSK9 inhibitors, SGLT2 inhibitors and icosapent ethyl, all of which are PBS-listed for atherosclerotic cardiovascular disease.
- The applicability of downstream semaglutide treatment benefits in the trial to the Australian setting is uncertain given initiation of GLP-1 analogues was not permitted in patients who developed diabetes during the trial.

6.50 The PBAC considered that the claim of superior comparative effectiveness in reducing major adverse cardiovascular events in patients with eCVD was reasonable.

6.51 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.52 The resubmission presented a stepped economic evaluation of semaglutide compared to placebo in patients with established cardiovascular disease who were overweight or obese. The resubmission presented the results for three alternative patient populations based on different BMI thresholds: ≥27 kg/m^2 (consistent with the key trial population), ≥35 kg/m^2 and ≥40 kg/m^2. The economic evaluation was based on the SELECT trial with additional modelled data. The economic evaluation was presented as a cost effectiveness/cost utility analysis.

6.53 The economic evaluation was based on patient populations without pre-existing diabetes. No cost effectiveness estimates were provided for patients with pre-existing diabetes.

6.54 Key components of the economic evaluation are summarised in Table 9.

Table 9: Key components of the economic evaluation

Component	Description
Type of analysis	Cost effectiveness/cost utility analysis
Outcomes	Events avoided, life years, quality adjusted life years
Time horizon	25 years
Methods used to generate results	Markov cohort analysis
Treatments	Semaglutide or placebo.
Model structure	A combination of 16 cardiovascular disease health states (established cardiovascular disease, MI only, S only, HF only, UA only, CR only, MI+S, MI+HF, MI+UA, MI+CR, S+HF, S+UA, S+CR, HF+UA, HF+CR, UA +CR), 2 diabetes health states (diabetes, no diabetes) and 6 chronic kidney disease health states (stage 1, 2, 3a, 3b, 4, 5) as well as cardiovascular death and non-cardiovascular death
Cycle length	28 days (half cycle correction)
Patient characteristics and circumstances of use	Baseline age, sex, BMI and chronic kidney disease stage were based on reported baseline values from the combined treatment arms of the SELECT population (established cardiovascular disease with BMI ≥27 kg/m^2) as well as the subgroup populations with baseline BMI ≥35 kg/m^2 and baseline BMI ≥40 kg/m^2. Treatment discontinuation rates for semaglutide and the distribution of semaglutide maintenance doses were based on the overall population of the SELECT trial.
Transition probabilities	The risk of treatment discontinuation in the semaglutide arm was based on a *post hoc* analysis of the overall population from the SELECT trial which censored discontinuations that occurred within 30 days prior to end-of-treatment or end-of-trial period. The risk of adverse events was estimated based on the reported event rates for serious adverse events in the overall population of the SELECT trial. The change in BMI over time was based on a *post hoc* analysis of the overall population in the SELECT trial (Ryan 2024). Time to optimal weight loss and time to weight regain after treatment discontinuation were estimated based on additional *post hoc* analyses of the SELECT trial. Weight loss in the placebo arm of the SELECT trial was assumed to represent the natural history of weight loss in older persons.

Component	Description
	The risks of cardiovascular death and non-fatal cardiovascular events in the first 3.5 years were based on reported incidence rates in the overall population of the SELECT trial. These risks were extrapolated based on the assumption of a constant risk over time that could be modified by additional risk multipliers for age (AIHW Heart, stroke and vascular disease report 2024), baseline BMI (Khan 2018) and diabetes status (Angoulvant 2021). The risk of non-cardiovascular death in the first 3.5 years was based on reported incidence rates in the overall population of the SELECT trial. These risks were extrapolated based on the assumption that the annualised incidence of events would remain constant over time. The risk of diabetes in the first 3.5 years was based on reported incidence rates in the overall population of the SELECT trial. These risks were extrapolated based on the assumption of a constant risk over time that could be modified by additional risk multipliers for baseline BMI (Zhang 2020). The risk of chronic kidney disease progression was based on the mean change in estimated glomerular filtration rate per year reported for the semaglutide and placebo arms of the overall SELECT trial population. These estimates were transformed into transition probabilities based on the assumption of a constant decline over time. The transition probabilities were modified by additional risk multipliers for baseline BMI (Kang 2020).
Utility values	Cardiovascular health state utility values were based on estimates from an Australian cost effectiveness study of icosapent ethyl versus placebo for the treatment of established cardiovascular disease (Gao 2019). Diabetes and weight-related disutility values were based on a sponsor-commissioned cross-sectional analysis of the relationship between BMI and EQ-5D-5L index scores in the general adult population using data from the 2017/2018 Health Survey for England (Luah 2024). Chronic kidney disease disutility values were based on values presented in an Australian cost of illness study for chronic kidney disease (Deloitte 2023). Disutility values for acute cardiovascular events were based on values reported in a published economic model assessing the cost effectiveness of treatments for dyslipidaemia in the UK treatment setting (Michaeli 2022). Disutility values for serious adverse events were based on estimates from various published sources.
Costs	Drug costs were estimated based on the proposed effective price of semaglutide. No other treatment costs were included for administration or adjunctive therapies. The costs of acute cardiovascular events, serious adverse events and terminal care were estimated by mapping each event to AR-DRG hospitalisation items. An average weighted cost was estimated based on the number of separations for each item and cost weights from the National Hospital Cost Data Collection Report, Public Sector Round 25 (2020–2021). Health state costs for cardiovascular disease were based on values reported in published Australian economic analyses (Marquina 2022, Savira 2021). Health state costs for patients with diabetes were based on a costing study of diabetes using data from the 2011-2012 update of the Australian Diabetes, Obesity and Lifestyle study (Lee 2018). Health state costs for chronic kidney disease were based on values presented in an Australian cost of illness study for chronic kidney disease (Deloitte 2023).
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3-1, p105 of the resubmission
Abbreviations: BMI, body mass index; CR, coronary revascularisation; HF, heart failure; MI, myocardial infarction; S, stroke; UA, unstable angina

6.55 The resubmission nominated a 25-year time horizon for the economic analysis on the basis that this was consistent with previous PBAC considerations of interventions for

established cardiovascular disease (July 2022 evolocumab submission; November 2023 icosapent ethyl submission). The ESC considered this was reasonable.

6.56 Patients enter the model in the established cardiovascular disease health state without diabetes but with chronic kidney disease at stage 1, 2 or 3a.

6.57 In each 4-weekly cycle patients can experience a non-fatal cardiovascular event (myocardial infarction, stroke, heart failure, unstable angina, coronary revascularisation), cardiovascular death or non-cardiovascular death. Non-fatal cardiovascular events were associated with both transient (acute) impacts as well as ongoing (chronic) impacts. The post-event history was only tracked using specific health states for the first two different modelled events (such as myocardial infarction only or myocardial infarction plus stroke). Beyond this, patients could continue to experience transient events and incur acute costs and disutilities but remained in the same health state. The pre-PBAC response addressed concerns that the utility weights for post event health states may include double counting by clarifying that the base case specification of the model applied a hierarchical (not multiplicative) approach to estimating quality of life losses in health states with multiple prior events. As such, only the quality of life decrement of the more severe event is used for the calculation of the utility weight for the post event health states.

6.58 Patients could also experience serious adverse events, develop diabetes, experience progression of chronic kidney disease, or experience weight loss/regain in each cycle. Patients who develop diabetes in the model were assumed to have a higher subsequent risk of cardiovascular disease. Weight loss/regain and chronic kidney disease progression were not directly linked to cardiovascular disease or mortality in model.

6.59 Additionally, patients in the semaglutide arm could discontinue treatment in each cycle. The resubmission assumed that patients who discontinue semaglutide would have the same risk as patients treated with placebo with the exception of a residual weight loss benefit for up to 2.36 years after treatment. Patients who discontinue therapy in the economic model were not allowed to re-initiate therapy. Therefore, the model does not provide any estimate of the cost effectiveness associated with multiple cycles of treatment.

6.60 The resubmission did not include any administration costs associated with using semaglutide. This may not be appropriate as semaglutide requires frequent GP visits during the titration period.

6.61 The resubmission assumed that the use of semaglutide would not be associated with increased use of other weight management services such as diet and exercise programs delivered by general practitioners and allied health professionals. It was unclear whether this assumption was reasonable.

6.62 Calculation errors related to the application of discontinuation rates and QALY losses in patients with a history of multiple events were identified during the evaluation. These errors were acknowledged by the sponsor and corrected in the evaluation.

6.63 Key drivers of the economic model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Cardiovascular risks	The risks of cardiovascular death and non-fatal cardiovascular events in the first 3.5 years were based on reported incidence rates in the overall population. These risks were extrapolated over time and to other alternative patient populations based on the assumption that the annualised incidence of events in the SELECT trial would remain constant over time. The resubmission implicitly assumed that semaglutide was associated with reductions in all modelled cardiovascular events. This assumption was not completely supported by clinical data from the SELECT trial which indicated a statistically significant reduction in the composite primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) and demonstrated nominally significant reductions for the individual events of non-fatal myocardial infarction and coronary revascularisation only. The PSCR argued that despite a lack of significance in some of the individual cardiovascular outcomes it was reasonable to include them in the economic model because of the different cost and health implications of each of them as individual events. The ESC acknowledged the arguments put forward by the PSCR but considered that the extent of impact on the ICER of inclusion of individual outcomes without significant results was difficult to justify and advised that additional multivariate sensitivity analyses excluding differences in these outcomes would be informative (see paragraph 6.79). The pre-PBAC response argued that a multivariate sensitivity analysis that completely removed the benefit of semaglutide on cardiovascular mortality on the basis of a p-value which was 0.07 may not be informative given this was a component of the primary endpoint. During the evaluation, it was noted that the global semaglutide economic model included other extrapolation options using parametric functions fitted to the SELECT trial data. These functions were disabled in the current model with the sponsor stating that they were unaware of any precedent for PBAC using survival functions to predict cardiovascular risk over time. Additionally, the sponsor noted that the constant risk approach was consistent with the approach used in another Australian model of semaglutide (Zomer 2024) and provides simplicity and transparency in the presentation of the transition probabilities and the associated risk multipliers incorporated into the model. Overall, it is unclear whether the use of constant risks represents the best fit to the available data and the natural history of established cardiovascular disease.	High, favours semaglutide
Chronic kidney disease risks	The risk of chronic kidney disease progression was based on the mean change in estimated glomerular filtration rate (eGFR) per year reported for the semaglutide and placebo arms of the overall SELECT trial population. The estimates were transformed into transition probabilities by estimating the total time it would take to transition from the maximum eGFR to the minimum eGFR in each chronic kidney disease stage using the reported mean changes for each arm. The resubmission assumed that the reported rate of change applied to all patients regardless of chronic kidney disease stage. The ESC agreed with the evaluation that this assumption was not reasonable and was not consistent with data from the SELECT trial which indicated that eGFR declines were only observed in patients with early stage disease while patients with more advanced kidney disease typically experienced stabilisation or improvement in eGFR values over time in both treatment arms (potentially related to the optimisation of background therapies). The PSCR acknowledged the differences in renal function impairment were only observed in patients with early stages of kidney disease in the SELECT trial and provided a sensitivity analysis for a scenario which stabilises the probability of CKD progression in both arms of the model, increasing the ICER for the base case subgroup from $[redacted][1] to $[redacted][1] per QALY gained.	High, favours semaglutide

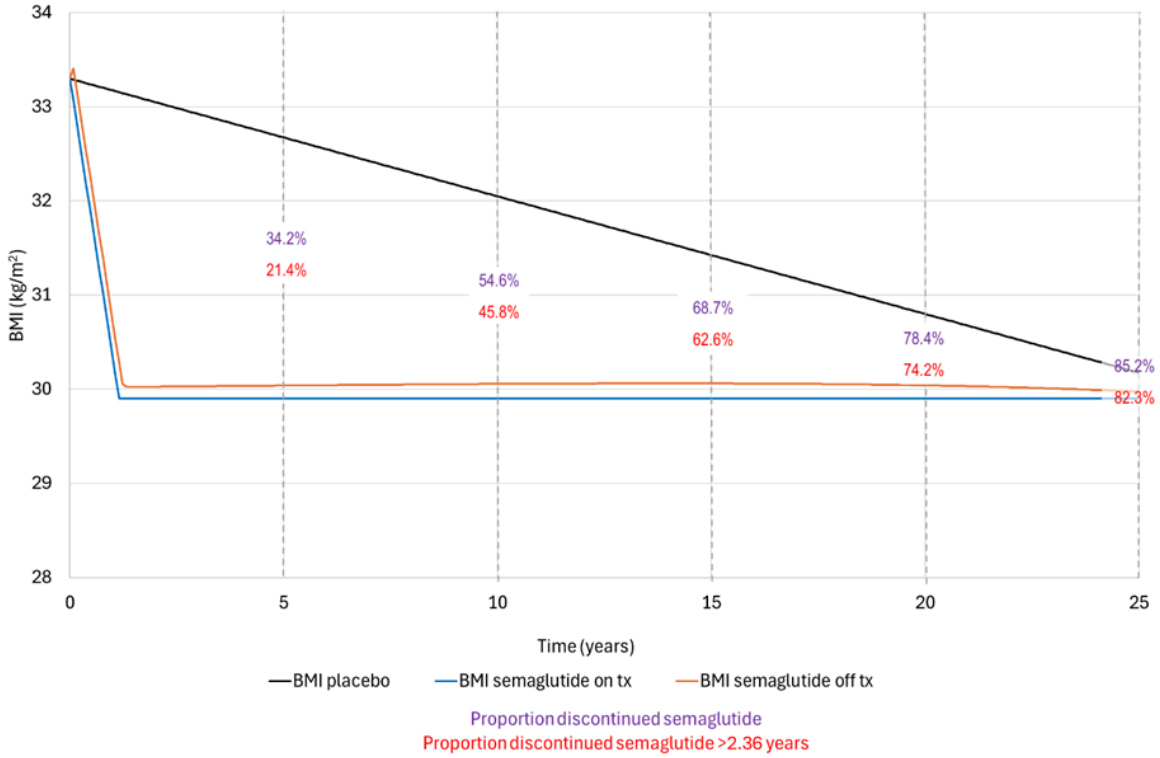
Description	Method/Value	Impact
Risk multipliers	Age-based risk multipliers for cardiovascular events were based on the incidence of events reported in the AIHW Heart, stroke and vascular disease report 2024 (using data from 2021). The resubmission did not adequately justify the mapping of AIHW data to modelled events in the economic evaluation. In particular, some estimates appeared implausible, such as female patients aged ≥85 years having 3.5 times the risk of a coronary revascularisation procedure compared to females aged 55-64 years which is not consistent with other available data. Diabetes-based risk multipliers for cardiovascular events were based on a retrospective longitudinal study of hospitalisation records for patients hospitalised in France in 2013 (Angoulvant 2021). The publication excluded patients with pre-existing cardiovascular disease and therefore the generalisability of results to patients with established cardiovascular disease was unclear. Additionally, the analysis only included hospitalised patients and therefore may not be reflective of the broader population. Further, given the rapidly changing landscape for diabetes treatment it was unclear whether these results would be applicable to current Australian clinical practice. BMI-based risk multipliers for cardiovascular events (Khan 2018), diabetes (Zhang 2020) and chronic kidney disease (Kang 2020) were derived from various published sources. The resubmission did not adequately justify the use of external data sources to inform BMI-based risk multipliers given the availability of data from the SELECT trial. The PSCR acknowledged that the risk of cardiovascular events was not consistently higher in subgroup populations with higher baseline BMI values in the SELECT trial. The PSCR suggested that this may be a limitation of the SELECT trial rather than a real world effect as the trial was not necessarily powered to detect increasing cardiovascular risk with increasing BMI. As such, the PSCR stated that the economic model introduced external BMI multipliers in order to reflect a higher clinical need and greater capacity to benefit in the higher BMI subgroups. The ESC considered the applicability of the published estimates (used to derive BMI, age and diabetes-based risk multipliers) to the model population with established cardiovascular disease was unclear. For example, the Khan 2018 publication used to inform the BMI-based risk multipliers for cardiovascular events reported the risk of developing cardiovascular disease in patients without pre-existing disease. The ESC noted that the combined effect of multiple risk multipliers was large (e.g. the risk of cardiovascular death increased up to 57 times the baseline risk in males and 152 times the baseline risk in females using risk multipliers). The PSCR claimed that the seemingly large multipliers (of 52 to 157) are, driven almost exclusively by age, with those over 85 years of age having a 25-to-66-fold increase in risk of CV death. The multipliers independent of age reaches a maximum of only 2.28 (for a diabetes patient with a BMI over 40). However, the ESC agreed with the evaluation that the application of multiple risk multipliers was not be appropriate as there is likely to be substantial double-counting of risks between different data sources. The ESC advised that the use of estimates directly from the SELECT trial have the added advantage of being based on established cardiovascular populations, capturing the implicit differences in BMI subgroup populations, as well as providing separate estimates for each modelled event.	High, favours semaglutide

Description	Method/Value	Impact
BMI-related QALY loss	BMI-related disutility values were estimated based on a sponsor-commissioned cross-sectional analysis of the relationship between BMI and EQ-5D-5L index scores in the general adult population using data from the 2017/2018 Health Survey for England (Luah 2024). The publication noted that the relationship between BMI and EQ-5D-5L utility scores represents an association rather than causation. The study authors noted that as a cross-sectional analysis the model does not capture the time dependency of effects (the impact of time spent in different BMI classes) nor can it identify the impact of weight change patterns (utility loss due to weight gain may be different from the utility gain from weight loss). Given these limitations, the resubmission did not adequately justify the use of this data source to inform disutility estimates given the availability of longitudinal EQ-5D-5L data from the SELECT trial which could allow the assessment of weight change patterns over time. The PSCR argued that high BMI is known to adversely affect quality of life and stated that this supports (along with the increased event risk multipliers used) the submission's premise that patients with higher BMI have a higher clinical need and capacity to benefit from treatment. As such, the PSCR argued that it was necessary to introduce external sources to ensure that this benefit of semaglutide was appropriately captured in the economic model. The ESC considered that, with the availability of EQ-5D-5L utility estimates from the SELECT trial, it was inappropriate to use less reliable estimates derived from external published sources. In particular, the ESC considered that applying cross sectional data longitudinally was a major source of uncertainty and was likely to overestimate effect. The ESC considered that double counting was highly likely with the approach taken. Additionally, a substantial proportion of the weight loss benefit attributed to semaglutide was due to the inappropriate modelling of time dependent BMI changes in a Markov cohort model which resulted in a substantial overestimation of ongoing BMI treatment effects in patients who have discontinued semaglutide treatment (see Figure 3).	High, favours semaglutide
Coronary revascularisation costs	The cost associated with coronary revascularisation events was based on the weighted average hospitalisation cost ($57,438 per event) derived using AR-DRG items. The estimate used in the resubmission included items for heart valve replacements (a different procedure) but did not include items related to percutaneous coronary interventions (the most common type of coronary revascularisation procedure). Overall, the costs for coronary revascularisation procedures do not appear to be plausible particularly in comparison to the costs of other acute cardiovascular events (>4 times the cost of a myocardial infarction event). The PSCR argued that all event costs in the model were inherently underestimated because they only include the cost of the hospital episode and none of the costs of treatment or managing the event that happen outside of the hospital stay. The ESC agreed with the evaluation that the costs of coronary revascularisation procedures used in the model were not plausible.	High, favours semaglutide

Source: Constructed during the evaluation.
Abbreviations: AIHW, Australian Institute for Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; BMI, body mass index; eGFR, estimated glomerular filtration rate; PBAC, Pharmaceutical Benefits Advisory Committee
The redacted values correspond to the following ranges:
[1] $15,000 to < $25,000

6.64 The average BMI over time in the modelled population with established cardiovascular disease and BMI ≥27 kg/m^2 (consistent with the SELECT overall trial population) is shown in Figure 3.

Figure 3: Average BMI of the modelled population with established cardiovascular disease and BMI ≥ 27kg/m^2



Source: 'Section 3 Workbook' provided with the resubmission
Abbreviations: BMI, body mass index; tx, treatment.

6.65 The resubmission claimed that patients discontinuing semaglutide treatment are assumed to return to placebo levels over 2.36 years following discontinuation. In response to an information request during the evaluation, the sponsor claimed that the apparent maintenance of the majority of weight loss in discontinued patients is due to the mixed cohort of patients, some of whom would have recently discontinued treatment and would still have the full weight loss effect, and others who have lost all their weight loss benefit. However, the ESC agreed with the evaluation that the traces show that, even when the majority of patients have discontinued semaglutide for more than 2.36 years, the vast majority of the BMI treatment effect is maintained, which is implausible. For example, at 15 years, the difference in BMI between semaglutide on-treatment patients and placebo patients is 1.5 kg/m^2 (29.9 versus 31.4 kg/m^2, respectively), and 1.3 kg/m^2 between semaglutide off-treatment patients and placebo patients (30.1 versus 31.4 kg/m^2, respectively). This indicates that, despite 62.6% of patients in the semaglutide arm having discontinued treatment at least 2.36 years ago (and who should have the BMI of placebo patients), 86.6% of the weight loss benefit is maintained in semaglutide patients off treatment. The ESC agreed with the evaluation that overall, the attempt to implement time-dependent effects in a Markov cohort structure resulted in the model substantially overestimating ongoing BMI treatment effects in patients who have discontinued semaglutide treatment. The ESC considered that the unexpected relationship between discontinuation rates and the

incremental cost effectiveness ratio (ICER), i.e. decreasing discontinuation rates increased the ICER and vice versa, arose in part due to this disconnect in the model (see Table 15). The pre-PBAC response stated that the model had been misinterpreted arguing that when all patients discontinue after 2 years the BMI of discontinuers displays an expected pattern (BMI returning to that of the placebo arm over 2.36 years). The PBAC noted that as the Markov cohort model cannot track how long each patient has been off treatment, it cannot accurately reflect the cumulative increase in BMI of patients over time. Instead, the model estimates the average BMI of the off-treatment cohort in each cycle using the weighted average BMI of all semaglutide patients (both on and off treatment) from the previous cycle, plus a small increment. This increment decreases over time as it is based on the difference between the placebo arm's BMI and the minimum BMI of patients on semaglutide treatment, and the placebo arm's BMI decreases over time. The PBAC noted this approach introduced a circular dependency: early in the model, the off-treatment cohort is small, and their estimated BMI is primarily driven by the larger on-treatment cohort, whose BMI remains lower due to semaglutide treatment effects. As a result, the estimated BMI of the off-treatment group remains artificially and persistently low, even though patients are expected to gain weight after treatment discontinuation. This underestimation persists due to the circular dependency, and the smaller BMI increment applied over time as the proportion of patients discontinuing treatment increases.

6.66 The results of the modelled economic evaluation are summarised in Table 11.

Table 11: Results of the modelled economic evaluation

	Semaglutide	Placebo	Increment
Established cardiovascular disease and BMI ≥27 kg/m²			
Costs	$[redacted][3]	$96,461	$[redacted][1]
Life years	11.6252	11.2920	0.3332
QALYs	9.2340	8.7708	0.4633
Incremental cost per life year gained			**$[redacted]**
Incremental cost per QALY gained			**$[redacted][2]**
Established cardiovascular disease and BMI ≥35 kg/m²			
Costs	$[redacted][3]	$100,773	$[redacted][1]
Life years	11.6244	11.2707	0.3537
QALYs	8.8870	8.3271	0.5599
Incremental cost per life year gained			**$[redacted]**
Incremental cost per QALY gained			**$[redacted][2]**
Established cardiovascular disease and BMI ≥40 kg/m²			
Costs	$[redacted][4]	$109,380	$[redacted][1]
Life years	10.8112	10.4048	0.4064
QALYs	7.9007	7.3100	0.5907
Incremental cost per life year gained			**$[redacted][2]**
Incremental cost per QALY gained			**$[redacted][1]**
Incremental cost per QALY gained, CKD treatment effects limited to early-stage disease*			**$[redacted][1]**

Source: Table 3-95, p203 of the resubmission; 'Section 3 Workbook' provided with the resubmission.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; QALY, quality adjusted life year
*PSCR - Differences in CKD progression were maintained for transitions between CKD 1 to CKD 2 and CKD 2 to CKD 3, the risk of CKD progression for later stages in both treatment arms was set to be identical based on estimates from the semaglutide arm; BMI risk multiplier were included in this analysis
Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were used in the evaluation.
Note: Calculation errors related to the application of discontinuation rates and QALY losses in patients with history of multiple events were identified during the evaluation. These errors were acknowledged by the sponsor and corrected in the evaluation.
The redacted values correspond to the following ranges:
[1]*$15,000 to < $25,000*
[2]*$25,000 to < $35,000*
[3]*$95,000 to < $115,000*
[4]*$115,000 to < $135,000*

6.67 The PBAC has previously suggested acceptable ICERs for other related conditions including $15,000–$25,000 per QALY gained for icosapent ethyl for established cardiovascular disease with elevated triglycerides (icosapent ethyl PSD, March 2024 PBAC meeting), less than $25,000 to < $35,000 per QALY gained for evolocumab for established cardiovascular disease with elevated cholesterol levels and additional cardiovascular risk factors (evolocumab PSD July 2022 PBAC meeting); and $30,000 per QALY gained for tirzepatide for type 2 diabetes (tirzepatide PSD; November 2024 PBAC meeting).

6.68 Based on the economic model, treatment with semaglutide was associated with an incremental cost per QALY gained of $35,000 to < $45,000compared to placebo for the management of cardiovascular disease in patients who were overweight or obese (BMI ≥27 kg/m^2).

6.69 For every 1,000 overweight/obese patients with established cardiovascular disease who are treated with semaglutide versus placebo and followed up for 25 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- 162 fewer non-fatal cardiovascular events (primarily myocardial infarction and coronary revascularisation procedure).
- An average increase in survival of 8 months per patient due to a reduced risk of cardiovascular and non-cardiovascular death.
- Improved quality of life associated with weight loss and delayed progression of diabetes and chronic kidney disease (average increase of 0.2352 quality-adjusted life years per patient).
- Additional treatment ($20 million to < $30 million) and cardiovascular disease management costs ($0 to < $10 million) which were partially offset by decreased non-fatal cardiovascular events costs ($0 to < $10 million; primarily coronary revascularisation procedures) and chronic kidney disease management costs ($0 to < $10 million; primarily kidney failure).

6.70 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 cardiovascular disease in patients with Class 2/Class 3 obesity (BMI ≥35 kg/m^2).

6.71 For every 1,000 patients with Class 2/Class 3 obesity and established cardiovascular disease who are treated with semaglutide versus placebo and followed up for 25 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- 188 fewer non-fatal cardiovascular events (primarily myocardial infarction and coronary revascularisation procedure).
- An average increase in survival of 8 months per patient due to a reduced risk of cardiovascular and non-cardiovascular death.
- Improved quality of life associated with weight loss and delayed progression of diabetes and chronic kidney disease (average increase of 0.3425 quality-adjusted life years per patient).
- Additional treatment ($20 million to < $30 million) and cardiovascular disease management costs ($0 to < $10 million) which were partially offset by decreased non-fatal cardiovascular events costs ($0 to < $10 million; primarily coronary revascularisation procedures) and chronic kidney disease management costs ($0 to < $10 million; primarily kidney failure).

6.72 Based on the economic model, treatment with semaglutide was associated with an incremental cost per QALY gained of $15,000 to < $25,000 compared to placebo for the management of cardiovascular disease in patients with Class 3 obesity (BMI ≥40 kg/m^2).

6.73 For every 1,000 patients with Class 3 obesity and established cardiovascular disease who are treated with semaglutide versus placebo and followed up for 25 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- 226 fewer non-fatal cardiovascular events (primarily myocardial infarction and coronary revascularisation procedure).
- An average increase in survival of 9 months per patient due to a reduced risk of cardiovascular and non-cardiovascular death.
- Improved quality of life associated with weight loss and delayed progression of diabetes and chronic kidney disease (average increase of 0.3129 quality-adjusted life years per patient).
- Additional treatment ($20 million to < $30 million) and cardiovascular disease management costs ($0 to < $10 million) which were partially offset by decreased non-fatal cardiovascular events costs ($0 to < $10 million; primarily coronary revascularisation procedures) and chronic kidney disease management costs ($0 to < $10 million; primarily kidney failure).

6.74 The ESC noted that the differences between trial- and model-based estimates over the trial follow-up period were limited as the compounding effect of multiple risk multipliers primarily affects the later extrapolated period (e.g. age-based multipliers are not active during the first 3.5 years). However, when external BMI risk multipliers are introduced for the ≥35 and ≥40 kg/m^2 populations, the modelled estimates generally switched to being higher than the trial-based estimates, particularly for coronary revascularisation events, cardiovascular death and non-cardiovascular death, as the external risk multipliers were not reflective of the SELECT trial data. See Tables 12–14 below. The ESC considered the disconnect between the trial outcomes and the modelled cardiovascular outcomes were not well justified, as there was no trend for more events avoided in the SELECT subgroups by higher BMI.

Table 12: Comparison of trial-based and modelled cardiovascular events in patients with a BMI ≥27 kg/m^2

Health outcomes	Trial-based estimates[a]			Modelled estimates[b]		
	Semaglutide	Placebo	Increment	Semaglutide	Placebo	Increment
Cardiovascular events per 1,000 patients over 3.5 years						
Non-fatal myocardial infarction	30	44	-14	27	38	-10
Non-fatal stroke	20	21	-1	18	19	-1
Hospitalisation/urgent care for heart failure	18	21	-3	11	14	-3
Hospitalisation for unstable angina	14	16	-2	13	14	-1
Coronary revascularisation	67	91	-24	56	73	-17
Cardiovascular death	27	31	-4	25	30	-5
Non-cardiovascular death	18	24	-6	17	22	-5

Source: 'Section 3 Workbook' provided with the resubmission

a Calculated based on reported trial-based event rates for total events (includes initial and subsequent events) for the ITT population × 3,500 years of observation time (1,000 patients with 3.5 years follow-up)

b Calculated based on 1,000 modelled patients and a time horizon of 3.5 years. The model used direct estimates from the SELECT trial during this period based on the reported incidence rates (initial event only) with an additional risk multiplier for diabetes (age multipliers do not affect the first 3.5 years of the model and no BMI multipliers are applied to ITT population)

Table 13: Comparison of trial-based and modelled cardiovascular events in patients with a BMI ≥35 kg/m²

Health outcomes	Trial-based estimates[a]			Modelled estimates[b]		
	Semaglutide	Placebo	Increment	Semaglutide	Placebo	Increment
Cardiovascular events per 1,000 patients over 3.5 years						
Non-fatal myocardial infarction	34	46	-12	30	42	-12
Non-fatal stroke	24	24	0	20	21	-1
Hospitalisation/urgent care for heart failure	24	30	-6	12	15	-3
Hospitalisation for unstable angina	10	10	0	15	16	-1
Coronary revascularisation	67	82	-15	62	81	-19
Cardiovascular death	34	34	0	27	33	-6
Non-cardiovascular death	22	24	-2	16	22	-6

Source: 'Section 3 Workbook' provided with the resubmission

a Calculated based on reported trial-based event rates for total events (includes initial and subsequent events) for the BMI ≥35 kg/m2 subgroup population × 3,500 years of observation time (1,000 patients with 3.5 years follow-up)

b Calculated based on 1,000 modelled patients and a time horizon of 3.5 years. The model used direct estimates from the SELECT trial ITT population during this period based on the reported incidence rates (initial event only) with additional risk multipliers for diabetes and BMI (age multipliers do not affect the first 3.5 years of the model)

Table 14: Comparison of trial-based and modelled cardiovascular events in patients with a BMI ≥40 kg/m²

Health outcomes	Trial-based estimates[a]			Modelled estimates[b]		
	Semaglutide	Placebo	Increment	Semaglutide	Placebo	Increment
Cardiovascular events per 1,000 patients over 3.5 years						
Non-fatal myocardial infarction	27	41	-14	47	65	-18
Non-fatal stroke	24	27	-3	31	33	-2
Hospitalisation/urgent care for heart failure	22	28	-6	19	24	-5
Hospitalisation for unstable angina	2	10	-8	23	25	-2
Coronary revascularisation	53	68	-15	97	125	-28
Cardiovascular death	35	37	-2	43	51	-8
Non-cardiovascular death	26	28	-2	16	21	-5

Source: 'Section 3 Workbook' provided with the resubmission

a Calculated based on reported trial-based event rates for total events (includes initial and subsequent events) for the BMI ≥40 kg/m2 subgroup population × 3,500 years of observation time (1,000 patients with 3.5 years follow-up)

b Calculated based on 1,000 modelled patients and a time horizon of 3.5 years. The model used direct estimates from the SELECT trial ITT population during this period based on the reported incidence rates (initial event only) with additional risk multipliers for diabetes and BMI (age multipliers do not affect the first 3.5 years of the model)

6.75 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 15.

Table 15: Results of key sensitivity analyses

Analyses	ICER (% change from base case)		
	CVD and BMI ≥27 kg/m²	CVD and BMI ≥35 kg/m²	CVD and BMI ≥40 kg/m²
Base case	$ [redacted][4]	$ [redacted][4]	$ [redacted][3]*
Discount rate (base case: 5% for benefits and costs)			
3.5% discount rate	$ [redacted][4] ([redacted]%)	$ [redacted][3] ([redacted]%)	$ [redacted][3] ([redacted]%)
0% discount rate	$ [redacted][3] ([redacted]%)	$ [redacted][3] ([redacted]%)	$ [redacted][3] ([redacted]%)
Time horizon (base case: 25 years)			
Lifetime (100 - baseline age)	$ [redacted][4] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted][3] ([redacted]%)
10 years	$ [redacted][7] ([redacted]%)	$ [redacted][6] ([redacted]%)	$ [redacted][5] ([redacted]%)
Baseline patient characteristics (base case: varied by BMI subgroup)			

Analyses	ICER (% change from base case)		
	CVD and BMI ≥27 kg/m²	CVD and BMI ≥35 kg/m²	CVD and BMI ≥40 kg/m²
Base case	$ [redacted]	$ [redacted]	$ [redacted]*
Reduce baseline age to 50 years	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Increase baseline age to 70 years	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Assume all patients have CKD stage 1	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Assume all patients have CKD stage 3a	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Circumstances of use (base case: semaglutide dose distribution and censored discontinuation rates based on SELECT trial)			
Assume all patients titrate to the 2.4 mg dose with no impact on modelled outcomes	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Assume equal use of the 1.7 mg and 2.4 mg dose strengths as maintenance doses (41.9% each) with no impact on modelled outcomes	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Increase discontinuation rates by 50%	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Decrease discontinuation rates by 50%	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Uncensored discontinuation rates	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Cardiovascular events (base case: trial-based incidence estimates for 3.5 years, with the assumption of constant risks for subsequent cycles with additional risk multipliers for age [AIHW], BMI [Khan 2018] and diabetes status [Angoulvant 2021])			
Constant risks for whole model duration	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for non-fatal myocardial infarction using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for non-fatal stroke using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for heart failure using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for unstable angina using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for coronary revascularisation using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No difference in risk between arms for cardiovascular death using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Using constant risks over model duration, only include differences in risk for outcomes included in the primary composite (non-fatal MI, non-fatal stroke, cardiovascular death)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Using constant risks over model duration, only include differences in risk for outcomes with nominally significant results (non-fatal MI, coronary revascularisation)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No additional risk multipliers for age	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No additional risk multipliers for diabetes	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No additional risk multipliers for BMI	-	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Use BMI risk multipliers based on SELECT trial	-	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Double the risk for subsequent events	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove all risk multipliers	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Diabetes (base case: trial-based incidence estimates for 3.5 years, with the assumption of constant risks for subsequent cycles with additional risk multipliers for BMI [Zhang 2020])			
No difference in risk between arms for diabetes using constant risk for whole model duration[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)

Analyses	ICER (% change from base case)		
	CVD and BMI ≥27 kg/m²	CVD and BMI ≥35 kg/m²	CVD and BMI ≥40 kg/m²
Base case	$ [redacted]	$ [redacted]	$ [redacted]*
Use BMI risk multipliers based on SELECT trial	-	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No additional risk multipliers for BMI	-	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Chronic kidney disease (base case: probabilities of transitioning between health states based on the assumption of a constant decrease in eGFR over time from the SELECT trial with additional risk multipliers for BMI [Kang 2020])			
No difference in risk between arms for CKD progression[a]	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove CKD module (no risk of progression in either arm)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
No additional risk multipliers for BMI	-	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Body mass index (base case: mean change with semaglutide treatment and time to optimal weight loss based on the SELECT trial, assumption that weight loss remains stable while patients remain on therapy, estimated weight gain after discontinuation based on a post hoc analysis of the time to 100% regain to baseline levels; assume natural history decrease in BMI per year based on the placebo arm of the SELECT trial)			
No residual BMI benefit after treatment discontinuation	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Utility/disutility values (base case: various sources)			
Use baseline utility score from the SELECT trial	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove cardiovascular health state disutility values (all states the same as established cardiovascular disease)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove acute cardiovascular event disutility values	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove diabetes health state disutility values	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove CKD health state disutility values	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Remove BMI disutility values	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Health state costs (base case: various published sources)			
Double CVD health state costs based on a history of myocardial infarction	$ [redacted] ([redacted]%)	$ [redacted] [redacted]%)	$ [redacted] ([redacted]%)
Halve CVD health state costs based on a history of myocardial infarction	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Double CVD health state costs based on a history of stroke (including established cardiovascular disease)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Halve CVD health state costs based on a history of stroke (including established cardiovascular disease)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)
Double CKD stage 5 disease management costs	$ [redacted] ([redacted]%)	$ [redacted] [redacted]%)	$ [redacted] [redacted]%)
Halve CKD stage 5 disease management costs	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] [redacted]%)
Event costs (base case: hospitalisation costs based on AR-DRG items)			
Double coronary revascularisation acute event costs	$ [redacted] ([redacted]%)	$ [redacted] [redacted]%)	$ [redacted] ([redacted]%)
Halve coronary revascularisation acute event costs	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)	$ [redacted] ([redacted]%)

Source: 'Section 3 Workbook' provided with the resubmission.

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

*an updated scenario removing a difference in later stage CKD progression was provided in the PSCR, and the base case increased to $15,000 to < $25,000/QALY gained. Differences in CKD progression were maintained for transitions between CKD 1 to CKD 2 and CKD 2 to CKD 3, the risk of CKD progression for later stages in both treatment arms was set to be identical based on estimates from the semaglutide arm; BMI risk multiplier were included in this analysis[a] Risks based on the placebo arm of the SELECT trial

Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were used in the evaluation.

Note: Calculation errors related to the application of discontinuation rates and QALY losses in patients with history of multiple events were identified during the evaluation. These errors were acknowledged by the sponsor and corrected in the evaluation.

The redacted values correspond to the following ranges:

[1]*$0 to < $5,000*
[2]*$5,000 to < $15,000*
[3]*$15,000 to < $25,000*
[4]*$25,000 to < $35,000*
[5]*$35,000 to < $45,000*
[6]*$45,000 to < $55,000*
[7]*$55,000 to < $75,000*

6.76 The results of the sensitivity analyses indicated that the model was most sensitive to the discount rate, time horizon, baseline patient characteristics, circumstances of use (dose distribution and treatment persistence), incidence of diabetes (particularly the flow-on impact to cardiovascular risk), risk of CKD progression, risk of cardiovascular events (particularly coronary revascularisation procedures and cardiovascular death), BMI disutility value, cardiovascular and kidney failure health state costs, and cardiovascular risk multipliers for age, BMI and diabetes status.

6.77 During the evaluation, additional multivariate sensitivity analyses were conducted using data from the SELECT trial to inform baseline utility values and BMI-based risk multipliers. The analyses also assessed the impact of removing the CKD progression module (which was inconsistent with trial data from SELECT), as well as halving the cost of coronary revascularisation procedures (which were substantially overestimated in the base case analysis). The results of the multivariate analyses are shown in Table 16.

Table 16: Results of multivariate sensitivity analyses conducted during the evaluation

Analyses	ICER (% change from base case)		
	CVD and BMI ≥27 kg/m²	CVD and BMI ≥35 kg/m²	CVD and BMI ≥40 kg/m²
Base case	$ [redacted][2]	$ [redacted][2]	$ [redacted][1]
Step 1: Baseline utility scores from the SELECT trial	$ [redacted][2] (- [redacted]%)	$ [redacted][2] ([redacted]%)	$ [redacted][1] (+ [redacted]%)
Step 2: As for Step 1, and including BMI risk multipliers for cardiovascular events and diabetes based on data from the SELECT trial	$ [redacted][2] (- [redacted]%)	$ [redacted][2] (+ [redacted]%)	$ [redacted][2] (+ [redacted]%)
Step 3: As for Step 2, and removing the CKD module (no risk of progression in either arm)	$ [redacted][3] (+ [redacted]%)	$ [redacted][3] (+ [redacted]%)	$ [redacted][3] (+ [redacted]%)
Step 4: As for Step 3, and halving coronary revascularisation acute event costs	$ [redacted][3] (+ [redacted]%)	$ [redacted][3] (+ [redacted]%)	$ [redacted][3] (+ [redacted]%)

Source: 'Section 3 Workbook' provided with the resubmission.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year
Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were used in the evaluation.
Note: Calculation errors related to the application of discontinuation rates and QALY losses in patients with history of multiple events were identified during the evaluation. These errors were acknowledged by the sponsor and corrected in the evaluation.
The redacted values correspond to the following ranges:
[1]*$15,000 to < $25,000*
[2]*$25,000 to < $35,000*
[3]*$35,000 to < $45,000*

6.78 The multivariate analyses based on data from the SELECT trial indicated that there are minimal differences in the cost effectiveness of treatment between BMI subgroups ≥35 kg/m^2 and ≥40 kg/m^2, and both of these groups appear more cost effective than the overall population, largely due to the impact of BMI-related QALY loss. The

multivariate analyses were associated with substantially higher incremental cost effectiveness ratios than estimated in the base case (and modified base case as per PSCR) analysis.

6.79 The ESC considered the multivariate analyses proposed by the evaluation were informative and suggested reversion to baseline BMI in patients who have discontinued semaglutide treatment was also required. Additional consideration should also be given to including the following Steps in the MVSA to assess the impact on the ICERs: only including differences in risk for outcomes with nominally significant results (for the ITT population this included non-fatal myocardial infarction and coronary revascularisation only), and removing external published sources for BMI disutility values. The PBAC noted the pre-PBAC response raised that the SELECT trial was not adequately powered to detect differences in individual CV outcomes. It was also noted in the response that for the evolocumab submission, the PBAC had previously considered the modelling of differences in CV death without a statistically significant difference in the pivotal FOURIER trial [HR: 1.05 (95% CI 0.88-1.25); Table 7 of the July 2022 evolocumab PSD. The PBAC noted that the pre-PBAC response had claimed that costs included in the model were conservative and that in particular the cost of stroke was underestimated. The PBAC noted that multivariate sensitivity analyses that decreased the costs of myocardial infarction and increased the cost of stroke events had a minimal impact on the ICER (data not shown) and advised that no variation from the resubmission base case was required for these costs.

6.80 The ESC also requested the Sponsor provide ICERs for the multivariate analyses specified in paragraph 6.79 for BMI 27–35 kg/m^2, and 35–40 kg/m^2 sub-groups (rather than ≥27 kg/m^2, and ≥35 kg/m^2, which includes the higher categories). Alternatively, to at least assess the impact of respecifying the subgroups on the base case ICERs. The pre-PBAC response stated that ICERs for the BMI 27–35 kg/m^2 and 35–40 kg/m^2 sub-groups could not be calculated based on the ESC's respecified multivariate analyses. The pre-PBAC response reported ICERs of $35,000 to < $45,000 and $25,000 to < $35,000 per QALY gained for the BMI 27–35 kg/m^2 and 35–40 kg/m^2 sub-groups respectively using submission base case assumptions (which apply CVD, diabetes and CKD diabetes risk inflators based on Khan (2018), Zhang (2020) and Kang (2020) respectively, and BMI-based disutilities based on Luah (2024).) These ICERs show the impact of expanding beyond the submission base case which was for the BMI ≥40 kg/m^2 group, which had an ICER of $15,000 to < $25,000 per QALY gained.

6.81 The PBAC requested the additional multivariate analyses shown in Table 17.

Table 17 Results of multivariate sensitivity analyses requested by PBAC

Analyses	ICER (% change from base case)		
	CVD and BMI ≥27 kg/m²	CVD and BMI ≥35 kg/m²	CVD and BMI ≥40 kg/m²
Base case	**$** [redacted]	**$** [redacted][2]	**$** [redacted][1]
Step 1: Baseline utility scores from the SELECT trial	$[redacted][2] (-[redacted]%)	$[redacted][2] ([redacted]%)	$[redacted][1] (+[redacted]%)
Step 2: As for Step 1, and including BMI risk multipliers for cardiovascular events and diabetes based on data from the SELECT trial	$[redacted][2] (-[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)
Step 3: As for Step 2, and halving coronary revascularisation acute event costs	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)
Step 4: As for Step 3, with CKD treatment effects limited to early-stage disease (consistent with PSCR)	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)
Step 5a: As for Step 4, with no retained BMI treatment effects after discontinuation	$[redacted][2] (+[redacted]%)	$[redacted] (+[redacted]%)	$[redacted] (+[redacted]%)
Step 5b: As for Step 4, with 10% of BMI treatment effects maintained after discontinuation	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted] (+[redacted]%)
Step 5c: As for Step 4, with 20% of BMI treatment effects maintained after discontinuation	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted][2] (+[redacted]%)

Source: 'Section 3 Workbook' provided with the resubmission.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were used in the commentary.

Note: Calculation errors related to the application of discontinuation rates and QALY losses in patients with history of multiple events were identified during the evaluation. These errors were acknowledged by the sponsor and corrected in the commentary.

The redacted values correspond to the following ranges:

[1]*$15,000 to < $25,000*

[2]*$25,000 to < $35,000*

[3]*$35,000 to < $45,000*

Drug cost/patient/year

6.82 The estimated drug costs for semaglutide per patient per year are summarised in Table 18.

Table 18: Drug cost per patient per year for semaglutide

	SELECT	Economic model	Financial estimates
Includes titration phase	Yes	Yes	No
Maintenance dose distribution	0.25 mg: 4.69% 0.5 mg: 4.98% 1.0 mg: 6.56% 1.7 mg: 7.40% 2.4 mg: 76.37%	0.25 mg: 4.69% 0.5 mg: 4.98% 1.0 mg: 6.56% 1.7 mg: 7.40% 2.4 mg: 76.37%	0.25 mg: 4.69% 0.5 mg: 4.98% 1.0 mg: 6.56% 1.7 mg: 7.40% 2.4 mg: 76.37%
Cost per 28 days (effective DPMQ)	-	0.25 mg: $[redacted] 0.5 mg: $[redacted] 1.0 mg: $[redacted] 1.7 mg: $[redacted] 2.4 mg: $[redacted]	0.25 mg: $[redacted] 0.5 mg: $[redacted] 1.0 mg: $[redacted] 1.7 mg: $[redacted] 2.4 mg: $[redacted]
Proportion of patients on treatment (censored for end-of-trial/end-of-treatment period)	12 months: 87% 24 months: 82% 36 months: 76%	12 months: 88% 24 months: 82% 36 months: 76%	Uptake, discontinuation and reinitiation abstracted to a combined utilisation rate
Cost per year	-	First year: $[redacted] Subsequent years: $[redacted] (declines over time with treatment discontinuation)	All years: $[redacted] (applies to all treated patients)

Source: Constructed during the evaluation using the Section 3 and Section 4 Excel workbooks provided with the resubmission.
Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were used in the evaluation.

Estimated PBS usage & financial implications

6.83 The resubmission was considered by DUSC.

6.84 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing semaglutide on the PBS/RPBS for patients with established cardiovascular disease who are overweight or obese.

6.85 The key inputs used to derive the financial implications are presented in Table 19.

Table 19: Key inputs for the financial estimates

Data	Value/source	Comment
Prevalence of CVD and overweight/ obesity	Prevalence of CVD and BMI ≥27 kg/m^2 increasing from 2.62% in Year 1 to 2.81% in Year 6. Prevalence of CVD and BMI ≥35 kg/m^2 increasing from 0.71% in Year 1 to 0.76% in Year 6. Prevalence of CVD and BMI ≥40 kg/m^2 increasing from 0.28% in Year 1 to 0.30% in Year 6. Australian National Health Survey (2022). Based on the proportion of patients who were overweight (25 to <30 kg/m^2) or had Class I (30 to <35 kg/m^2), Class 2 (35 to <40 kg/m^2) or Class 3 (≥40 kg/m^2) obesity AND a self-reported history of heart attack, stroke or diseases of the arteries, arterioles and capillaries. 60% of patients in the overweight BMI category were assumed to have BMI values ≥27 kg/m^2. Estimates do not include adjustments for the lower BMI thresholds (-2.5 kg/m^2 than other populations) in patients of Asian or Aboriginal and Torres Strait Islander descent. An annualised increase in the prevalence of overweight/ obesity in the Australian population (relative 1.4% increase per year) was estimated based on the difference in the proportion of the Australian population with obesity in the 2012 National Health Survey (27.5%) versus the 2022 National Health Survey (31.6%).	This was appropriate but may underestimate the eligible patient population given that approximately 20% of the Australian population (based on the 2021 Census) identify themselves as Aboriginal or Torres Strait Islander (3.2%), East Asian (10.9%) or Central/Southern Asian (6.5%) and who would have lower BMI thresholds than the general population. DUSC commented that if 20% of the Australian population would be eligible under a lower BMI threshold, then the number of eligible patients would be underestimated. DUSC noted that although the prevalence of obesity has been increasing, the prevalence of CVD has been declining over time[3,4]. DUSC considered the use of GLP-1 analogues for T2D could prevent primary CVD and that the rate of decrease of CVD could increase over time.

[3] Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts [Internet]. Canberra: Australian Institute of Health and Welfare, 2024 [cited 2025 Oct. 17]. Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts

[4] Heart Foundation. Statistics and information on cardiovascular disease in Australia [Internet]. 2025 [cited 2025 Oct. 17]. Available from: https://www.heartfoundation.org.au/your-heart/evidence-and-statistics/key-stats-cardiovascular-disease

Data	Value/source	Comment
Semaglutide utilisation rate	Utilisation rate in patients with CVD and BMI ≥27 kg/m^2 increasing from [redacted]% in Year 1 to [redacted]% in Year 6. Utilisation rate in patients with CVD and BMI ≥35 kg/m^2 increasing from [redacted]% in Year 1 to [redacted]% in Year 6. Utilisation rate in patients with CVD and BMI ≥40 kg/m^2 increasing from [redacted]% in Year 1 to [redacted]% in Year 6. Assumption. The resubmission claimed that this was informed by market research and the sponsor's experience in other international settings (no documentation was provided with the resubmission).	Given the abstract nature of the utilisation rates (which covers treatment initiation, discontinuation and re-initiation) it was not possible to validate these estimates with other published data sources. DUSC noted that there was no market research, information from private sales, or PBS Ozempic data or international data provided with the resubmission and that these rates could not be validated. DUSC considered the utilisation rates for BMI>40 were overestimated and the rates for BMI >27 were underestimated in later years.
Semaglutide scripts per patient per year	12: Assumption. Based on one script per month	DUSC noted that a patient would need 13 scripts for a full year of treatment but considered it unlikely that this would correctly estimate the number of scripts supplied per year. DUSC considered that this value should be modelled from the semaglutide for T2D PBS data (7.0 to 8.5) to account for patients initiating, pausing or discontinuing treatment through each year.
Dose distribution of semaglutide scripts	0.25 mg: 4.69%; 0.5 mg: 4.98%; 1.0 mg: 6.56%; 1.7 mg: 7.40%; 2.4 mg: 76.37% Based on the distribution of doses at the end of the titration period (Week 20) in the SELECT ITT population (patients with CVD and BMI ≥27). As a simplified prevalence model, the utilisation estimates are based on maintenance doses and do not account for dose titration.	It was unclear whether the dose distribution observed in the trial setting would be representative of doses used in clinical practice. Additionally, it was unclear whether the subgroup populations with higher baseline BMI would have the same dose distribution as the overall trial population. DUSC commented that most observational studies have shown slower time to reach to maintenance doses than seen in clinical trials. DUSC considered the proportion of 2.4 mg use was overestimated. DUSC considered the proportion of patients on lower doses could be as high as 30%, but more likely 20-25% in the Australian context. DUSC commented that the dose

Data	Value/source	Comment
		distribution will change over time as years 2–6 will include more people on maintenance vs titration doses. DUSC suggested it may be preferable to model and account for titration doses among initiators.

Source: Section 4, pp213-224 of the resubmission
Abbreviations: BMI, body mass index; CVD, cardiovascular disease

6.86 The estimated utilisation and financial implications of listing semaglutide on the PBS/RPBS for patients with established cardiovascular disease who were overweight or obese is summarised in Table 20.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients with CVD and BMI ≥27 kg/m²						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net PBS/RPBS cost	[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]	[redacted]
Patients with CVD and BMI ≥35 kg/m²						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net PBS/RPBS cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with CVD and BMI ≥40 kg/m²						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net PBS/RPBS cost	$[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: 'Section 4 Workbook' provided with the resubmission
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.
Note: The effective DPMQs estimated for semaglutide in the resubmission were calculated using a non-standard methodology. During the evaluation, the sponsor confirmed the calculation of revised effective DPMQs estimated using standard methods. These revised prices were

used in the commentary.
The redacted values correspond to the following ranges:
[1]30,000 to < 40,000
[2]40,000 to < 50,000
[3]50,000 to < 60,000
[4]60,000 to < 70,000
[5]70,000 to < 80,000
[6]80,000 to < 90,000
[7]90,000 to < 100,000
[10]100,000 to < 200,000
[11]200,000 to < 300,000
[12]400,000 to < 500,000
[13]500,000 to < 600,000
[14]600,000 to < 700,000
[15]700,000 to < 800,000
[16]800,000 to < 900,000
[17]1,000,000 to < 2,000,000
[18]2,000,000 to < 3,000,000
[19]3,000,000 to < 4,000,000
[14]$90 million to < $100 million
[15]$100 million to < $200 million
[16]$200 million to < $300 million
[17]$300 million to < $400 million
[18]$400 million to < $500 million
[19]$500 million to < $600 million
[20]$600 million to < $700 million
[21]$700 million to < $800 million
[19]$900 million to < $1 billion

6.87 The corrected estimated total cost to the PBS/RPBS for semaglutide in patients with established cardiovascular disease who were overweight or obese (BMI ≥27 kg/m^2) was $300 million to < $400 million in Year 1, increasing to $900 million to < $1 billion in Year 6, with a cumulative cost of > $1 billion over the first 6 years of listing.

6.88 The corrected estimated total cost to the PBS/RPBS for semaglutide in patients with established cardiovascular disease and Class 2/3 obesity (BMI ≥35 kg/m^2) was $100 million to < $200 million in Year 1, increasing to $300 million to < $400 million in Year 6, with a cumulative cost of > $1 billion over the first 6 years of listing.

6.89 The corrected estimated total cost to the PBS/RPBS for semaglutide in patients with established cardiovascular disease and Class 3 obesity (BMI ≥40 kg/m^2) was $90 million to < $100 million in Year 1, increasing to $100 million to < $200 million in Year 6, with a cumulative cost of $900 million to < $1 billion over the first 6 years of listing.

6.90 DUSC considered the estimates presented in the submission to be overestimated. The main issues were:

- The estimated number of supplied scripts per patient per year was overestimated, as it did not account for patients initiating, pausing or discontinuing treatment through each year. DUSC considered that this value should be modelled from the semaglutide for type 2 diabetes PBS data (7.0 to 8.5 scripts per patient per year).
- There is a high degree of uncertainty associated with estimated utilisation rates which could not be validated against other data sources. DUSC considered the utilisation rates for BMI ≥40 kg/m^{2}were overestimated and the rates for BMI ≥27 kg/m^{2}were underestimated in later years.

- DUSC considered the proportion of patients who would be treated with 2.4 mg of semaglutide per week was overestimated.

6.91 The pre-PBAC response provided additional sensitivity analyses which varied the following inputs (Table 21):

- Lower script volume per patient modelled between 7.5 to 8.5 scripts per year, based on 2024/2025 PBS data for semaglutide in type 2 diabetes.
- Lower and higher assumed utilisation rates in the BMI ≥40 kg/m^2 and BMI ≥27 kg/m^2 subgroups, respectively.
- Different proportional utilisation of available strengths to reflect slower and less complete titration.

Table 21 Pre-PBAC response sensitivity analyses to the financial estimates

Analysis	Details	6-year cost to PBS/RPBS		
		BMI ≥27 kg/m^2	BMI ≥35 kg/m^2	BMI ≥40 kg/m^2
Base Case		$[redacted][6]	$[redacted][6]	$[redacted][4]
1	Volume: 7.5 scripts per patient per year	$[redacted][6]	$[redacted]	$[redacted][2]
2	Volume: 8.0 scripts per patient per year	$[redacted][6]	$[redacted][6]	$[redacted][2]
3	Volume: 8.5 scripts per patient per year	$[redacted][6]	$[redacted][6]	$[redacted][2]
4 [a]	Annual uptake rates	$[redacted][6]	$[redacted][6]	$[redacted][3]
5 [b]	Proportion of patients by dose	$[redacted][6]	$[redacted][6]	$[redacted][4]
Multi-way	3+4	$[redacted][6]	$[redacted][6]	$[redacted][1]
	4+5	$[redacted][6]	$[redacted][6]	$[redacted][3]
	3+5	$[redacted][6]	$[redacted][6]	$[redacted][2]
	3+4+5	$[redacted][6]	$[redacted][5]	$[redacted][1]

Source: Table 1 pre-PBAC response

[a] Uptake rates adjusted differently by BMI group ((≥27 kg/m^2/ ≥35 kg/m^2/ ≥40 kg/m^2). Base case – 2026: [redacted]%/[redacted]%/[redacted]%; 2027: [redacted]%/[redacted]%/[redacted]%; 2028: [redacted]%/[redacted]%[redacted]%; 2029: [redacted]%/[redacted]%/[redacted]%; 2030: [redacted]%/[redacted]%/[redacted]%; 2031: [redacted]%/[redacted]%/[redacted]%. Sensitivity analysis – 2026: [redacted]%/[redacted]%/[redacted]%; 2027: [redacted]%/[redacted]%/[redacted]%; 2028: [redacted]%/[redacted]%/[redacted]%; 2029: [redacted]%/[redacted]%/[redacted]%; 2030: [redacted]%/[redacted]%/[redacted]%; 2031: [redacted]%/[redacted]%/[redacted]%

[b] Dose: 0.25/0.5/1mg: 6%; 1.7mg: 12%; 2.4mg: 70%

The redacted values correspond to the following ranges:

[1]$400 million to < $500 million

[2]$500 million to < $600 million

[3]$700 million to < $800 million

[4]$800 million to < $900 million

[5]$900 million to < $1 billion

[6]> $1 billion

Quality Use of Medicines

6.92 The resubmission stated that the sponsor will undertake pharmacovigilance/data collection activities and provide education support to patients, doctors, pharmacists and other healthcare professionals. A detailed quality use of medicines strategy report was commissioned by the sponsor and provided in the documents accompanying the resubmission.

6.93 DUSC commented that completing the titration schedule in 16 weeks could be difficult for people with gastrointestinal adverse effects. If these patients were dispensed higher dose pens they will likely calculate the number of clicks needed to dispense a lower dose of semaglutide, which DUSC considered was a quality use of medicines

issue. The pre-PBAC response noted that the quality use of medicines concern regarding click counting applies to the FlexTouch device. The pre-PBAC response clarified that this issue does not arise with the pre-filled single dose device which the sponsor is requesting listing for in this resubmission.

Financial Management – Risk Sharing Arrangements

6.94 The resubmission acknowledged that some form of risk-sharing arrangement would be required given the magnitude and nature of the uncertainties surrounding the financial implications of a PBS/RPBS listing of semaglutide for adult patients with established cardiovascular disease who were overweight or obese. However, the resubmission claimed it would be premature to propose a firm framework for such an agreement in the absence of PBAC advice on other critical aspects of the resubmission.

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

7 PBAC Outcome

7.1 The PBAC recommended semaglutide for patients with established cardiovascular disease (eCVD) with obesity, in patients who have already experienced a cardiovascular event including myocardial infarction, stroke, or symptomatic peripheral arterial disease. The PBAC was satisfied that semaglutide provides, for some patients, a significant improvement in efficacy over standard of care. The PBAC considered that restricting the eCVD population to a Body Mass Index (BMI) ≥35 kg/m^2 or ≥32.5 kg/m^2 individuals of Asian or Aboriginal or Torres Strait Islander ethnicity was appropriate as this represented a high priority population. The PBAC agreed with the ESC that revisions to the economic model were required including amendments to BMI treatment effects after discontinuation and advised that the resulting incremental cost-effectiveness ratio (ICER) was unacceptably high. The PBAC advised that a reduction in the cost per patient was required to achieve an acceptable incremental cost-effectiveness ratio. The PBAC considered the risk of use outside of the proposed patient population (particularly in patients with eCVD and with a BMI of less than 35 kg/m^2) was very high and advised that a risk sharing arrangement was required to adequately manage the risk to the Commonwealth.

7.2 The PBAC noted the input from individuals, health care professionals and organisations which highlighted the benefits of treatment with semaglutide for patients who have eCVD with obesity. The PBAC noted the input highlighted the high cost of semaglutide in the private market as a barrier to access. The PBAC noted the input from health care professionals and organisations emphasising that adjustments to eligibility criteria such as the BMI threshold be considered for Aboriginal and Torres Strait Islander peoples given the disproportionate health effects of eCVD with obesity in this population. Finally, the PBAC noted that a large proportion of the input from individuals was focused on a broader PBS listing for weight loss outside of those with eCVD with obesity, which supported the PBAC's view that the risk of use outside of the proposed indication was high.

7.3 The PBAC acknowledged that, although there are effective treatments on the PBS for patients with eCVD, there remains a residual secondary cardiovascular risk and a high need for effective therapies, particularly for patients also living with obesity.

7.4 With respect to the proposed restriction, the PBAC advised that:

- An Authority Required (telephone/electronic) listing for initial, continuing and grandfather treatment phases was appropriate.
- The indication for use is established atherosclerotic cardiovascular disease with patients required to have a confirmed diagnosis of at least one of myocardial infarction, prior stroke or the presence of symptomatic peripheral arterial disease. The PBAC considered it appropriate that symptomatic peripheral arterial disease should be evidenced by intermittent claudication with ankle-brachial index <0.85 at rest or peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease.
- Use be restricted to individuals with a BMI ≥35 kg/m^2 at the time of treatment initiation unless they are of Asian or Aboriginal or Torres Strait Islander ethnicity. The PBAC advised that a BMI of ≥ 32.5 kg/m^2 was appropriate for individuals of Asian or Aboriginal or Torres Strait Islander ethnicity.
- The PBAC noted the ESC advice regarding the recent publication in The Lancet Diabetes & Endocrinology[5] in which the definition and diagnostic criteria of clinical obesity was moving away from solely relying on BMI, and there was a consensus statement regarding diagnostic criteria for clinical obesity in adults with respect to CVD. However, the PBAC advised that as BMI was still widely used at this point in time, and the SELECT clinical trial relied on BMI measurements, additional criteria within the PBS restriction to define obesity such as waist circumference, would not be required for this population.
- The treatment must be used in conjunction with standard of care associated with both the management of established atherosclerotic cardiovascular disease and the prevention of future cardiovascular events, including dietary therapy and exercise.
- The restriction should not include the presence or absence of pre-existing diabetes as part of the eligibility criteria. However, patients must not be undergoing concomitant PBS-subsidised treatment with another GLP-1 receptor agonist or a dipeptidyl peptidase-4 inhibitor (DPP4) inhibitor.

[5] Rubino, F. et al; "Definition and diagnostic criteria of clinical obesity", *The Lancet Diabetes & Endocrinology*, Volume 13, Issue 3, 2025, Pages 221-262

- The intent of the initial treatment phase is to allow dose titration to be completed within 16 weeks where possible. However, the Committee acknowledged that some patients require a slower dose titration and advised that a mechanism to allow medical practitioners to be able to request up to 2 repeats per semaglutide strength be included in the initial treatment restriction in order to provide a maximum of 3 months' therapy per titrating dose.
- Noting that 16.23% of patients in the SELECT trial used lower dose strengths as maintenance, and it was expected that lower maintenance doses would also be used in clinical practice, the Committee advised that the continuing treatment restriction should include sufficient repeats for the lower dose strengths (0.25, 0.5 and 1.0 mg), to be used for maintenance dosing.
- In terms of grandfathering patients, the initial treatment phase would allow patients currently on titration dosing for semaglutide (up to a maximum of 1.7 mg weekly) to transition to PBS-subsidised therapy. The Committee advised that a 'Grandfather – maintenance dosing' treatment phase listing would be appropriate to allow eligible patients currently receiving non-PBS subsidised maintenance dosing of semaglutide, to transition to PBS-subsidised therapy. Patients would qualify for the Grandfather restriction once only with the restriction ceasing to operate from 12 months after the date specified in the clinical criteria.

7.5 The PBAC noted that flow on changes to GLP-1 RA listings for type 2 diabetes mellitus would be required to only allow access under the subsequent PBS prescription phase if received semaglutide under the first PBS-prescription phase.

7.6 The PBAC considered placebo plus standard of care management was the appropriate main comparator, noting that semaglutide will be used as an add-on treatment to standard of care management.

7.7 The PBAC recalled that in March 2022 and November 2023 the Committee had considered semaglutide for the treatment of severe obesity based on the findings of the STEP clinical trial program (see paragraphs 2.4 to 2.8). The PBAC noted that, in contrast to March 2022 and November 2023 submissions, the resubmission was based on the SELECT trial which compared cardiovascular outcomes in patients with semaglutide to placebo in patients with eCVD who were obese or overweight. The PBAC agreed with the resubmission that, given the comprehensively revised patient population, the current application was not a continuation of the March 2022 and November 2023 listing requests for use in patients with overweight and obesity. Rather, the PBAC acknowledged it was a *de novo* application for the recently approved TGA indication for secondary prevention of cardiovascular events.

7.8 The PBAC noted the SELECT study was a large randomised controlled trial (n=17,504) that compared semaglutide to placebo and considered the risk of bias was low. All patients in the trial received 'optimised' background therapy for cardiovascular risk

factors as well as lifestyle counselling. The PBAC noted that, although the majority of patients in SELECT trial met the criteria for prediabetes (see paragraph 6.11), patients with pre-existing diabetes were specifically excluded. The PBAC noted that the efficacy and cost-effectiveness of treating patients with eCVD and diabetes was not directly assessed in this submission. However, if semaglutide was considered cost-effective in the eCVD with obesity population, then the cost-effectiveness of semaglutide could be inferred for patients who also had type 2 diabetes. The rationale for this is as follows: patients with diabetes would be at higher baseline risk of a future cardiac event; the evidence in primary prevention of cardiovascular outcomes for GLP-1 therapies supported the use of semaglutide in type 2 diabetes patients with high cardiovascular risk (see Table 8, semaglutide PSD, November 2019 PBAC meeting); it was biologically plausible that these patients would benefit from treatment; it would ensure equitable access for high risk populations; consumer input advocated for the inclusion of T2DM; the cardiovascular benefit from the SELECT trial was only partly attributable to weight loss and therefore the lower weight loss seen in type 2 diabetes patients from the STEP trials (see Table 4, semaglutide PSD, March 2022 PBC meeting) was not relevant.

7.9 The PBAC noted that treatment with semaglutide in the SELECT trial was associated with a statistically significant decreased risk of major adverse cardiovascular events compared to placebo (HR 0.80, 95% CI 0.72, 0.90). Semaglutide was associated with a reduction in body weight over time compared to placebo (treatment difference -8.5% (95% CI -8.8, -8.3). However, the PBAC noted that pre-specified mediation analyses suggested that the reduction in cardiovascular events in the trial could only be partially attributed to reductions in weight (see paragraph 6.18). The PBAC noted that although a reduction in death from cardiovascular causes was observed, the results failed superiority testing as it did not achieve statistical significance (HR 0.85, 95% CI 0.71, 1.01). Superiority testing was not performed for remaining secondary endpoints in the hierarchy. Acknowledging this, the PBAC noted that semaglutide was associated with a decreased risk of all-cause death (HR 0.81, 95% CI 0.71, 0.93), non-fatal myocardial infarction (HR 0.72, 95% CI 0.61, 0.85) and coronary revascularisation (HR 0.77, 95% CI 0.68, 0.87) compared to placebo. The PBAC considered the evidence supported a claim of superior comparative efficacy in reducing major adverse cardiovascular events in patients with eCVD. However, the PBAC considered the benefits observed in clinical practice may be more modest than in the pivotal trial due to likely slower titration, lower maintenance doses and increased discontinuation rates, as is currently seen in patients using semaglutide in clinical practice overseas (see paragraph 6.12).

7.10 The PBAC noted that treatment with semaglutide was associated with a lower incidence of serious adverse events, primarily due to fewer serious cardiac disorder events. However, a higher percentage of patients in the semaglutide arm experienced serious gastrointestinal disorders (3.9% compared to 1.6%) and discontinued treatment compared to placebo due to adverse events (16.6% compared to 8.2%), primarily due to the more frequent occurrence of gastrointestinal disorders such as

nausea, diarrhoea and vomiting. The PBAC noted that adverse events leading to treatment discontinuation were more frequent during the dose escalation phase but continued to occur throughout the trial period. The PBAC considered that the claim of inferior comparative safety was reasonable.

7.11 The PBAC noted the resubmission presented an economic evaluation for three alternative patient populations based on different BMI thresholds: ≥27 kg/m^2 (consistent with the key trial population), ≥35 kg/m^2 and ≥40 kg/m^2. The economic evaluation was based on the SELECT trial with additional modelled data. The PBAC noted ESC advice that the disconnect between the trial outcomes and the modelled cardiovascular outcomes was not well justified and the PBAC considered the model would only be reliable for decision-making with revisions to several of the model inputs:

- The ED-5D-5L utility estimates from the SELECT trial should be used to inform the model rather than external published sources which increased the uncertainty in the model and introduced a risk of double counting.
- BMI risk multipliers used in the model for cardiovascular events and diabetes should be based on data from the SELECT trial as there is likely to be substantial double-counting of risks between different data sources in the approach used in the resubmission.
- Chronic kidney disease (CKD) treatment effects should be limited to early-stage disease (consistent with the PSCR).
- The costs of coronary revascularisation acute event costs used in the model were not plausible and should be halved.
- No BMI treatment effects should be retained after discontinuation.

The PBAC noted the additional multivariate sensitivity analyses undertaken for the Committee in Table 17. Noting the similarity in the ICERs reported for Step 5a, Step 5b and Step 5c, the PBAC considered that the Step 5a multivariate analyses addressed the main concerns with the economic analysis raised by the Committee.

7.12 The PBAC advised that the Step 5a multivariate analyses in Table 17 should be used to determine the cost effectiveness of semaglutide. The PBAC noted there was little difference in the ICERs for the BMI thresholds of ≥35 kg/m^2 ($35,000 to < $45,000 per QALY gained) and ≥40 kg/m^2 ($35,000 to < $45,000 per QALY gained). The ICER for the BMI threshold ≥27 kg/m^2 was only slightly higher ($35,000 to < $45,000 per QALY gained), however, the PBAC noted this difference would be much larger when looking at the subgroups as mutually exclusive groups (as per paragraph 6.80) rather than overlapping groups. The PBAC considered it would be appropriate to limit PBS access to patients with excess adiposity and as such a BMI ≥35 kg/m^2 was an appropriate threshold for a high priority group. The PBAC advised that an ICER of up to $25,000 per QALY, similar to that proposed in the PSCR for the submission base case (see Table 11) and also for ICERs accepted for similar indications in eCVD (see paragraph 6.67), would be appropriate. This ICER was further supported by the inclusion of type 2

diabetes patients in the PBS listing as, although the inclusion of these patients could be inferred to be cost-effective (see 7.8), it added to the clinical uncertainty in the ICER. The PBAC advised a reduction in treatment cost per patient per year would therefore be required to achieve cost effectiveness.

7.13 The PBAC noted DUSC advice that the estimates presented in the submission were overestimated. The PBAC agreed with DUSC that the estimated number of supplied scripts per patient per year was high and advised that this should be reduced to 8.5 scripts per patient per year, which better reflected expected discontinuation and adherence in clinical practice and aligned with PBS data for semaglutide use for type 2 diabetes. The PBAC noted this was at the upper end of the range suggested in the DUSC advice (7.0 – 8.5).

7.14 The PBAC noted DUSC advice that utilisation rates for the BMI threshold ≥40 kg/m^2 were overestimated and the rates for the BMI threshold ≥27 kg/m^2 were underestimated in later years. The PBAC accepted the revised utilisation rates across the BMI subgroups proposed in the pre-PBAC response. The PBAC also agreed with DUSC that the estimated proportion of patients who would be treated with 2.4 mg of semaglutide per week was higher than would likely be seen in clinical practice and accepted the pre-PBAC response revisions to this input (the proportion of use of the dose of 2.4 mg semaglutide was reduced from 76.37% to 70%). The PBAC noted the pre-PBAC response provided revised financial estimates based on the DUSC advice. The PBAC noted that incorporating these revisions the pre-PBAC response reported the cost over 6 years as > $1 billion, $900 million to < $1 billion and $400 million to < $500 million for the BMI thresholds of ≥27 kg/m^2, ≥35 kg/m^2 and ≥40 kg/m^2 respectively (see Table 21). The PBAC noted the financial estimates would reduce with the reduction in treatment cost per patient per year required to achieve an ICER of $25,000 per QALY and would need to be confirmed during implementation, given they were not evaluated.

7.15 The PBAC considered the risk of use outside of the proposed patient population (particularly in patients with eCVD and with a BMI of less than 35 kg/m^2) was very high and considered a risk sharing arrangement with 100% rebate above the caps would be required to mitigate the financial impact to the Commonwealth associated with use outside the restriction. The PBAC advised that the risk sharing subsidisation caps should be based on the revised financial estimates for the BMI threshold of ≥35 kg/m^2 outlined in paragraph 7.13.

7.16 The PBAC advised that semaglutide is suitable for prescribing by nurse practitioners, but only for continuing treatment and where patient care is shared with a medical practitioner.

7.17 Semaglutide should not be exempt from the Early Supply Rule as it has fixed dosing schedule, and it currently applies to similar drugs for chronic conditions.

7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met.

Specifically the PBAC found that in the circumstances of its recommendation for semaglutide:

i) The treatment is expected to provide a clinically relevant improvement in efficacy (in reducing major adverse cardiovascular events and all-cause mortality in patients with eCVD), over standard of care;

ii) The treatment is expected to address a high and urgent unmet clinical need for effective therapies for patients with established cardiovascular disease who are also living with obesity. The private expense of obtaining effective medicines to address residual cardiovascular risk and weight loss is prohibitive for many patients;

iii) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item as follows:

Initial treatment:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
SEMAGLUTIDE					
semaglutide 0.25 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	0	Wegovy
semaglutide 0.5 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	0	
semaglutide 1 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	0	
semaglutide 1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices	New	1	4	0	
Restriction Summary [new 1] / Treatment of Concept: [new 1A]					
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)				
	Prescribing rule level:				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				

	Administrative Advice: Abbreviations used in the restriction are as follows: DPP4 - dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 - glucagon-like peptide-1 receptor agonist
	Indication: Established atherosclerotic cardiovascular disease (eASCVD)
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have a confirmed diagnosis of at least one of (i) prior myocardial infarction, (ii) prior stroke (iii) symptomatic peripheral arterial disease (PAD)
	AND
	Clinical criteria:
	Patient must have/ have had a Body Mass Index greater than or equal to 35 kg/m2 at the time of treatment initiation with this drug,
	OR
	Patient must have/ have had a Body Mass Index greater than or equal to 32.5 kg/m2 at the time of treatment initiation with this drug, for people of either (i) Aboriginal, (ii) Torres Strait Islander, (iii) Asian ethnicity
	AND
	Clinical criteria:
	The treatment must be used in conjunction with standard of care associated with both (i) the management of eASCVD and (ii) the prevention of future CV events, including dietary therapy and exercise
	Treatment criteria:
	This treatment phase must be for dose titration purposes with the intent of completing the titration within 16 weeks of PBS and non-PBS subsidised therapy where possible, according to the dose escalation schedule in the Therapeutic Goods Administration (TGA) approved Product Information (PI).
	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment with any of: (i) another GLP-1 receptor agonist (ii) a DPP4 inhibitor
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing instructions: The patient's measured Body Mass Index at the time the first authority application is made must be documented in the patient's medical record.
	Prescribing instructions: At the time of the authority application, medical practitioners must request the appropriate number of repeats for patients who require a slower dose titration. ***Up to 2 repeats will be authorised to provide a maximum of 3 months' therapy per titrating dose***
	Prescribing instructions: Symptomatic peripheral arterial disease (PAD) should be evidenced by intermittent claudication with ankle-brachial index (ABI) <0.85 at rest or peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease.

Continuing treatment:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
SEMAGLUTIDE					
semaglutide 0.25 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	5	Wegovy
semaglutide 0.5 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	5	
semaglutide 1 mg/0.5 mL injection, 4 x 0.5 mL pen devices	New	1	4	5	
semaglutide 1.7 mg/0.75 mL injection, 4 x 0.75 mL pen devices	NEW	1	4	5	
semaglutide 2.4 mg/0.75 mL injection, 4 x 0.75 mL pen devices	NEW	1	4	5	

Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners
	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
	Prescribing rule level:
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Established atherosclerotic cardiovascular disease (eASCVD)
	Treatment Phase: Continuing Treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have completed the initial dose titration period with this drug for this condition
	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment with any of: (i) another GLP-1 receptor agonist (ii) a DPP4 inhibitor
	Treatment criteria:
	The treatment must be used in conjunction with standard of care associated with both (i) the management of CVD and (ii) the prevention of future CV events, including dietary therapy and exercise
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing instructions: Prescriber must ensure that patients are only receiving PBS subsidised treatment with one presentation of the maintenance dose of this drug at a time.

Grandfather treatment (maintenance doses):

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
SEMAGLUTIDE						
semaglutide 0.25 mg/0.5 mL injection, 4 x 0.5 mL pen devices		New	1	4	5	Wegovy
semaglutide 0.5 mg/0.5 mL injection, 4 x 0.5 mL pen devices		New	1	4	5	
semaglutide 1 mg/0.5 mL injection, 4 x 0.5 mL pen devices		New	1	4	5	
semaglutide 1.7 mg/0.5 mL injection, 4 x 0.5 mL pen devices		New	1	4	5	
semaglutide 2.4 mg/0.5 mL injection, 4 x 0.5 mL pen devices		New	1	4	5	
Restriction Summary [new] / Treatment of Concept: [new]						
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
	Prescribing rule level:					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Indication: Established atherosclerotic cardiovascular disease (eASVD)					
	Treatment Phase: Transitioning from non-PBS to PBS-subsided treatment **through maintenance doses** - Grandfather arrangements					
	Clinical criteria:					
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing]					
	AND					
	Clinical criteria:					
	Patient must have a confirmed diagnosis of at least one of (i) prior myocardial infarction, (ii) prior stroke (iii) symptomatic peripheral arterial disease (PAD)					
	AND					
	Clinical criteria:					
	Patient must have had a Body Mass Index greater than or equal to 35 kg/m2 at the time of treatment initiation with this drug,					
	OR					
	Patient must have had a Body Mass Index greater than or equal to 32.5 kg/m2 at the time of treatment initiation with this drug, for people of either (i) Aboriginal, (ii) Torres Strait Islander, (iii) Asian ethnicity					
	AND					
	Clinical criteria:					
	Patient must have completed the initial dose titration period with this drug for this condition					
	Treatment criteria:					
	Patient must not be undergoing concomitant PBS-subsidised treatment with any of: (i) another GLP-1 receptor agonist (ii) a DPP4 inhibitor					
	Treatment criteria:					
	The treatment must be used in conjunction with standard of care associated with both (i) the management of CVD and (ii) the prevention of future CV events, including dietary therapy and exercise					

	Population criteria:
	Patient must be at least 18 years of age
	Prescribing instructions: Symptomatic peripheral arterial disease (PAD) should be evidenced by intermittent claudication with ankle-brachial index (ABI) <0.85 at rest or peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease.
	Prescribing instructions: The patient's measured Body Mass Index at the time of initiating non-PBS subsidised treatment with this drug must be documented in the patient's medical record
	Prescribing instructions: Prescriber must ensure that patients are only receiving PBS subsidised treatment with one presentation of the maintenance dose of this drug at a time.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

8.2 Flow on changes to GLP1 RA listings (semaglutide and dulaglutide) for type 2 diabetes mellitus.

Add the following concept IDs to subsequent PBS prescription treatment phase:

	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the first PBS-prescription for this drug treatment phase;
	OR
	Patient must have previously received PBS-subsidised treatment with this drug for this condition commenced prior to 1 June 2024
PBS item codes to be changed:	
14163K 14846J 14150R	

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Novo Nordisk welcomes the PBAC's recommendation to list Wegovy® (semaglutide) on the PBS for the treatment of adult patients with established atherosclerotic cardiovascular disease (ASCVD) and obesity.

This recommendation, which applies to patients with a BMI ≥35 kg/m2 reflects the growing recognition of the importance of addressing cardiovascular risk in people living with obesity and marks an important first step toward securing more equitable access.

We extend our sincere appreciation to healthcare professionals, professional societies, peak bodies, patient organisations, patients and caregivers who provided invaluable input throughout the submission process.

Novo Nordisk will continue to work with the PBAC and the Department of Health to support timely, equitable and expanded access to Wegovy® (semaglutide) for adult patients living with established ASCVD and obesity.