7.04 TIRZEPATIDE

Injection 4.17 milligrams per mL (2.5 mg per dose) in multi-dose pre-filled pen, 4 doses, Injection 8.33 milligrams per mL (5 mg per dose) in multi-dose pre-filled pen, 4 doses, Injection 12.5 milligrams per mL (7.5 mg per dose) in multi-dose pre-filled pen, 4 doses, Injection 16.67 milligrams per mL (10 mg per dose) in multi-dose pre-filled pen, 4 doses, Injection 20.83 milligrams per mL (12.5 mg per dose) in multi-dose pre-filled pen, 4 doses, Injection 25 milligrams per mL (15 mg per dose) in multi-dose pre-filled pen, 4 doses, Mounjaro® KwikPen®, Eli Lilly Australia Pty Ltd.

1 Purpose of submission

1.1 The standard re-entry submission requested a General Schedule Authority Required listing (telephone/online) for initiation and an Authority Required (Streamlined) listing for continuation of tirzepatide for the treatment of adults with inadequately controlled type 2 diabetes mellitus.

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

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

Component	Description
Population	Adult patients with type 2 diabetes ~~with BMI ≥35 kg/m^2 or who identify as Aboriginal and Torres Strait Islander peoples~~ who are contraindicated, intolerant or inadequately controlled with SGLT2 inhibitors
Intervention	Tirzepatide 5 mg, 10 mg or 15 mg subcutaneous injection once weekly in combination with metformin, sulfonylurea and/or insulin*
Comparator	Semaglutide 0.5 mg or 1 mg subcutaneous injection once weekly in combination with metformin, sulfonylurea and/or insulin
Outcomes	Improved glycaemic control and body weight management leading to reduced macrovascular and microvascular complications, and associated morbidity and mortality associated with these complications.
Clinical claim	Tirzepatide 5 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety when compared with semaglutide 0.5 mg once weekly, when used in dual therapy with metformin. Tirzepatide 10 mg or 15 mg once weekly is superior in terms of efficacy and non-inferior in terms of safety when compared with semaglutide 1 mg once weekly, when used in dual therapy with metformin.

Source: Table 1, p7 of the resubmission

Note: Key changes compared to the November 2024 submission are marked using underline and ~~strikethrough~~

* The resubmission stated that the sponsor was uncertain whether the PBAC would like to consider the use of tirzepatide in combination with insulin with this resubmission, given it has not been previously evaluated.

2 Background

Registration status

2.1 The TGA approved tirzepatide on 22 December 2022 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.
- in addition to other medicinal products for the treatment of type 2 diabetes.

2.2 In September 2024, tirzepatide was TGA approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI):

- ≥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).

2.3 Tirzepatide is also currently under TGA evaluation 'For the treatment of symptomatic chronic heart failure'. The ESC noted that the TGA approved tirzepatide as a 'Treatment of moderate to severe obstructive sleep apnoea (repeated stopping and starting of breathing during sleep) in adults with obesity' in June 2025.

Previous PBAC consideration

2.4 The sponsor presented a Category 2 submission to the July 2023 PBAC meeting requesting a General Schedule Authority Required (Telephone/Online) listing for tirzepatide as dual therapy with metformin for adult patients with type 2 diabetes who

are contraindicated, intolerant or inadequately controlled with sodium glucose transporter-2 (SGLT2) inhibitors.

2.5 The PBAC did not recommend tirzepatide for the requested listing. The PBAC considered the primary reason for the outcome was due to the economic evaluation provided. The PBAC considered that the incremental cost-effectiveness ratio was high, inadequately justified, and uncertain. The PBAC advised that a revised economic model including a substantial price reduction would be required for the proposed listing to be considered cost-effective. The PBAC also considered that the financial impact was extremely high at the requested price and uncertain (para 7.1 and 7.2, tirzepatide Public Summary Document (PSD), July 2023 PBAC meeting).

2.6 In November 2024, the sponsor presented a standard re-entry submission requesting a General Schedule Authority Required listing (Written, endocrinologist only) for tirzepatide as dual therapy with metformin for adult patients with type 2 diabetes who are contraindicated, intolerant or inadequately controlled with SGLT2 inhibitors and who have comorbid severe obesity or who identify as Aboriginal and Torres Strait Islander. The PBAC did not recommend tirzepatide for the requested listing.

2.7 Table 2 summarises the outstanding matters of concern identified at the November 2024 PBAC meeting and how these were addressed in the resubmission.

Table 2: Summary of outstanding matters of concern

Outstanding matter of concern at the November 2024 PBAC meeting	How the resubmission addresses it
Restriction	
The PBAC considered that the treatment criteria restricting prescribing to a Written Authority in consultation with an endocrinologist represented inappropriate barriers to access tirzepatide. The PBAC also noted that physicians would want the ability to use tirzepatide in combination with a sulfonylurea and/or insulin (para 7.2 and 7.4, tirzepatide PSD, November 2024 PBAC meeting).	The resubmission modelled the proposed restriction for tirzepatide based on the current PBS restriction for semaglutide which has a lower authority level (Initiation Authority Required – Online/Telephone; Continuation: Streamlined), broader prescriber type (medical practitioner) and broader list of co-administered therapies (combination with metformin, sulfonylurea and/or insulin). The resubmission stated that the proposal to allow tirzepatide use in combination with insulin was optional as the resubmission noted that this combination has not undergone a full clinical and economic assessment.

Outstanding matter of concern at the November 2024 PBAC meeting	How the resubmission addresses it
Economic model	
The ESC stated that a revised base case should include: - switching to insulin/insulin intensification when HbA1c >8.0%. - apply UKPDS biomarker drift for all biomarkers and test using more recent data. The ESC also suggested testing the replacement of baseline utility, BMI, nausea and hypoglycaemia while on first-line therapy with the SUPRPASS-2 estimates or removing some of the utility effects from weight gain/loss in year one to account for potential double counting (para 6.93, tirzepatide PSD, November 2024 PBAC meeting). The PBAC noted that a revised economic model was included in the pre-PBAC response which allowed insulin switching when HbA1c >7.5% and allowed biomarker drift for BMI, systolic blood pressure and heart rate while on insulin. However, the PBAC considered the pre-PBAC response economic model did not adequately address the concerns raised by ESC with inadequate justification provided to refute the requested changes (para 7.12 and 7.13, tirzepatide PSD, November 2024 PBAC meeting)	The updated economic model included in the resubmission allowed switching to insulin/insulin intensification when HbA1c >8.0%. The resubmission did not address the requested changes to biomarker drift or the use of SURPASS-2 utility values.
The PBAC also reaffirmed its July 2023 advice that an ICER in the order of $30,000 per QALY would be appropriate (para 7.13, tirzepatide PSD, November 2024 PBAC meeting).	The proposed effective price for tirzepatide was reduced to achieve an incremental cost per QALY of approximately $30,000 for the comparisons of tirzepatide 10 mg versus semaglutide 1 mg and tirzepatide 15 mg versus semaglutide 1 mg. However, the incremental cost per QALY gained for the comparison of tirzepatide 5 mg versus semaglutide 1 mg remained substantially higher than recommended.
Utilisation and financial impact of listing	
The PBAC noted ESC considered the resubmission's estimated utilisation and financial estimates were extremely high and uncertain and not sufficiently reliable for PBAC decision-making. The PBAC noted that revised net PBS/RPBS costs in the pre-PBAC response were substantially lower than estimated in the resubmission, primarily due to a reduction in the estimated size of the eligible population. However, the PBAC considered the financial impact remained extremely high at the prices proposed in the pre-PBAC response and considered the impact likely overestimated. In addition, the PBAC considered the estimated utilisation and financial implications in the pre-PBAC response were unable to be relied upon given they had not been evaluated (para 7.14, tirzepatide PSD, November 2024 PBAC meeting).	The financial estimates were substantially revised with a broader requested patient population and lower effective prices for tirzepatide.

Outstanding matter of concern at the November 2024 PBAC meeting	How the resubmission addresses it
Risk sharing arrangement	
The PBAC agreed with ESC that an RSA would be required given the high risk of use outside of the restriction into the chronic weight management indication. The PBAC noted that the pre-PBAC response proposed an RSA based on the revised financial estimates provided in the response. The PBAC considered the financial estimates were not sufficiently robust to be used for an RSA and advised that the arrangements proposed were unlikely to satisfactorily mitigate the risk to government of use outside of the proposed restriction (para 7.15, tirzepatide PSD, November 2024 PBAC meeting).	The resubmission proposed a new risk sharing arrangement consisting of a subsidisation cap with [redacted] use beyond the nominated caps (which were based on the financial estimates) rebated to [redacted].

Source: Table 2, p8 of the resubmission

Abbreviations: ESC, Economics Sub-Committee; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PSD, Public Summary Document; QALY, quality adjusted life year; RSA, risk-sharing arrangement; UKPDS, UK Prospective Diabetes Study

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

3 Requested listing

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

Initial and continuing treatment phase:

MEDICINAL PRODUCT medicinal product pack	Dispensed price for maximum quantity		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
	Published	Effective					
TIRZEPATIDE							
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL pen device	$397.53	$[redacted]	NEW	1	1	1	Mounjaro
tirzepatide 5 mg/0.6 mL injection, 2.4 mL pen device	$397.53	$[redacted]	NEW	1	1	5	
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL pen device	$543.41	$[redacted]	NEW	1	1	1	
tirzepatide 10 mg/0.6 mL injection, 2.4 mL pen device	$543.41	$[redacted]	NEW	1	1	5	
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL pen device	$689.31	$[redacted]	NEW	1	1	1	
tirzepatide 15 mg/0.6 mL injection, 2.4 mL pen device	$689.31	$[redacted]	NEW	1	1	5	

Restriction Summary [new 1] / Treatment of Concept: [new 2]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/electronic)

Prescribing rule	**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: Diabetes mellitus type 2
	Treatment Phase: First PBS-prescription for this drug
	Clinical criteria:
	The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin,
	AND
	Clinical criteria:
	The condition must be inadequately responsive to at least one of: metformin, a sulfonylurea, insulin,
	AND
	Clinical criteria:
	Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor;
	Patient must have a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor,
	~~**OR**~~
	~~Patient must have previously received a PBS-subsidised GLP-1 receptor agonist as treatment for type 2 diabetes mellitus~~
	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Administrative Advice: Definition: A HbA1c measurement greater than 7% despite treatment with the specified prior therapy/therapies indicates inadequate responsiveness. Where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2-week period indicates inadequate responsiveness. Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies: (a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies), (b) Red cell transfusion within the previous 3 months. Document HbA1c measurements (blood glucose measurements where relevant), as well as any intolerances/contraindications in the patient's medical records.
	Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 - sodium glucose transporter-2 inhibitor (drug names ending in 'flozin') DPP4 - dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 - glucagon-like peptide-1 receptor agonist
	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: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.
Restriction Summary [new 2] / Treatment of Concept: [new 3]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Indication: Diabetes mellitus type 2
	Treatment Phase: Subsequent PBS-prescriptions for *any GLP-1 receptor agonist including dual GIP/GLP-1 receptor agonist* ~~tirzepatide~~
	~~**Clinical criteria**~~
	~~The condition must be stable for the prescriber to consider the listed maximum quantity of this medicine suitable for this patient.~~
	Treatment criteria:
	Patient must not be ~~undergoing~~ *receiving concomitant* PBS-subsidised treatment for type 2 diabetes mellitus with any of:(i) a SGLT2 inhibitor, (ii) a DPP4 inhibitor~~, another~~ (iii) a GLP-1 receptor agonist
	Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 - sodium glucose transporter-2 inhibitor (drug names ending in 'flozin') DPP4 - dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 - glucagon-like peptide-1 receptor agonist
	Administrative Advice: Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.

Grandfather listing:

MEDICINAL PRODUCT medicinal product pack	**Dispensed price for maximum quantity**		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
	Published	**Effective**					
TIRZEPATIDE							
tirzepatide 2.5 mg/0.6 mL injection, 2.4 mL pen device	$397.53	$[redacted]	NEW	1	1	1	Mounjaro
tirzepatide 5 mg/0.6 mL injection, 2.4 mL pen device	$397.53	$[redacted]	NEW	1	1	5	
tirzepatide 7.5 mg/0.6 mL injection, 2.4 mL pen device	$543.41	$[redacted]	NEW	1	1	1	
tirzepatide 10 mg/0.6 mL injection, 2.4 mL pen device	$543.41	$[redacted]	NEW	1	1	5	
tirzepatide 12.5 mg/0.6 mL injection, 2.4 mL pen device	$689.31	$[redacted]	NEW	1	1	1	

tirzepatide 15 mg/0.6 mL injection, 2.4 mL pen device	$689.31	$[redacted]	NEW	1	1	5	

Restriction Summary [new 1] / Treatment of Concept: [new 2]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment)
Prescribing rule	**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: Diabetes mellitus type 2
	Treatment Phase: Transitioning from non-PBS to initial PBS-subsidised treatment - Grandfather arrangement
	Clinical criteria:
	Patient must have been receiving non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date].
	Clinical criteria:
	The treatment must be used in combination with at least one of: metformin, a sulfonylurea, insulin,
	AND
	Clinical criteria:
	The condition must have been inadequately responsive to at least one of: (i) metformin, (ii) a sulfonylurea, or (iii) insulin *prior to initiating treatment with this drug*
	AND
	Clinical criteria:
	Patient must not have achieved a clinically meaningful glycaemic response with an SGLT2 inhibitor *prior to initiating treatment with this drug*
	OR
	Patient must have had a contraindication/intolerance requiring treatment discontinuation of an SGLT2 inhibitor *prior to initiating treatment with this drug*
	~~**OR**~~
	~~Patient must have previously received a PBS-subsidised GLP-1 receptor agonist as treatment for type 2 diabetes mellitus *commenced prior to 1 June 2024 and accessed non-PBS subsidised treatment with this drug*~~
	~~**OR**~~
	~~The condition must be/have been inadequately responsive to combination treatment with a sulfonylurea plus metformin~~ prior to initiating treatment with this drug
	~~**OR**~~
	~~Patient must have a contraindication/intolerance requiring permanent treatment discontinuation to combination therapy with metformin plus a sulfonylurea~~ prior to initiating treatment with this drug
	~~**OR**~~
	~~The condition must be/have been inadequately responsive to combination treatment with insulin plus metformin (or insulin alone where the patient is contraindicated/intolerant to metformin) prior to initiating treatment with this drug~~
	~~**AND**~~

	Treatment criteria:
	Patient must not be undergoing concomitant PBS-subsidised treatment for type 2 diabetes mellitus with any of: an SGLT2 inhibitor, a DPP4 inhibitor, another GLP-1 receptor agonist
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e., where the dose is changing), mark the prescription that is intended for no further supply as 'Cancelled'.
	Administrative Advice: An inadequate response to prior therapy is defined as: A HbA1c measurement greater than 7% despite treatment with the specified prior therapy/therapies indicates inadequate responsiveness. Where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2-week period indicates inadequate responsiveness. Blood glucose monitoring is an alternative to HbA1c measurement where at least one of the following circumstances applies: (a) A clinical condition with reduced red blood cell survival (inclusive of haemolytic anaemias, haemoglobinopathies), (b) Red cell transfusion within the previous 3 months. Document HbA1c measurements (blood glucose measurements where relevant), as well as any intolerances/contraindications in the patient's medical records.
	Administrative Advice: Abbreviations used in the restriction are as follows: SGLT2 - sodium glucose transporter-2 inhibitor (drug names ending in 'flozin') DPP4 - dipeptidyl peptidase-4 inhibitor (drug names ending in 'gliptin') GLP-1 - glucagon-like peptide-1 receptor agonist
	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: *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Subsequent PBS-prescriptions for tirzepatide' criteria.*
	Administrative Advice: *This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.*
	Administrative Advice: *Where an SGLT2 inhibitor is being accessed through a PBS indication other than diabetes, the clinical criterion excluding concomitant treatment with an SGLT2 inhibitor is in relation to diabetes mellitus type 2 only.*

3.2 The proposed published prices for tirzepatide remain unchanged from the November 2024 submission. The resubmission requested a special pricing arrangement consisting of effective tiered prices: dispensed price for maximum quantity [DPMQ] of $[redacted] for the 2.5 mg and 5 mg doses; DPMQ of $[redacted] for the 7.5 mg and 10 mg doses; and DPMQ of $[redacted] for the 12.5 mg and 15 mg doses. The effective tiered prices requested in the November 2024 submission were: DPMQ of $[redacted] for 2.5 mg and 5 mg doses; DPMQ of $[redacted] for 7.5 mg and 10 mg doses; DPMQ of $[redacted] for 12.5 mg and 15 mg doses. The Pre-Sub-Committee Response (PSCR) proposed two alternative pricing proposals for determining the cost-effective price of

tirzepatide 5 mg (see paragraph 6.62). The pre-PBAC response indicated the price requested for tirzepatide 5 mg remained the same as the original price proposed in the resubmission (i.e. DPMQ $[redacted]).

3.3 The resubmission modelled the proposed PBS restriction for tirzepatide on the current PBS restriction for semaglutide which substantially broadened the target population (to all patients who are contraindicated, intolerant or inadequately controlled with SGLT2 inhibitors rather than high-risk subgroups) and addressed PBAC issues regarding inappropriate barriers to access with previous proposed restrictions.

3.4 The resubmission stated that the proposal to allow tirzepatide use in combination with insulin was optional as the resubmission noted that this combination has not undergone a full clinical and economic assessment. The PSCR provided a new analysis of the 10% PBS data assessing the relative proportion of glucagon-like peptide-1 (GLP-1) analogue use in combination with insulin. The PSCR argued that combination use with insulin has declined from 25% in 2018 to approximately 15% in 2025 and that it would likely continue to decline should tirzepatide be listed on the PBS. As such, the PSCR stated that a PBS indication for use of tirzepatide in combination with insulin was not required and proposed to exclude this indication from the PBS listing. The ESC noted that the estimates of GLP-1 use in combination with insulin could not be validated as the results were based on 'data on file' which was not presented with the response. In addition, the ESC considered the analysis should be interpreted with caution as it was based on relative estimates rather than absolute estimates. For example, based on the sponsor-commissioned analysis presented as an attachment with the PSCR (A7.2 Prospection Analysis 2025 (revised)) there were [redacted]0 patients using a GLP-1 analogue in June 2018 increasing to [redacted] in December 2024. These patient numbers and the proportions estimated in the PSCR suggest that GLP-1 use in combination with insulin has increased from approximately [redacted] patients in 2018 ([redacted] x 0.25) to [redacted] ([redacted] x 0.15) in 2024. The ESC also recalled that the PBAC had previously indicated that clinicians would want the ability to use tirzepatide in combination with a sulfonylurea and/or insulin (para 7.4, tirzepatide PSD, November 2024 PBAC meeting). The pre-PBAC response stated that use in combination with insulin was a low priority but supported retaining a PBS listing for this combination in line with previous PBAC advice.

3.5 The resubmission also included a grandfathering restriction (Authority Required – Online/Telephone) to allow PBS subsidised treatment in patients who had privately purchased or used tirzepatide in the clinical trial setting. The transitioning (i.e. 'grandfather') restriction allows patients who have previously not achieved a clinically meaningful response to an SGLT2 inhibitor or not achieved a clinically meaningful response to metformin in combination with insulin or a sulfonylurea to access tirzepatide treatment. The appropriateness of allowing grandfathered tirzepatide treatment in patients without a prior history of not achieving a clinically meaningful response to an SGLT2 inhibitor was unclear. The resubmission claimed that the number of patients accessing tirzepatide treatment under the proposed transitioning ('grandfather') provisions is likely to be small. The resubmission did not provide any

data to support this claim and the size of the tirzepatide private market for type 2 diabetes mellitus is unclear.

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

4 Population and disease

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

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

4.3 The population targeted in the resubmission was adult patients with type 2 diabetes who are contraindicated, intolerant or inadequately controlled with SGLT2 inhibitors.

4.4 Tirzepatide is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist.

4.5 Tirzepatide is self-administered as a subcutaneous injection. Available doses are 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg. The starting dose is 2.5 mg once weekly for 4 weeks, increasing to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after at least 4 weeks on the current dose. The recommended doses are 5 mg, 10 mg and 15 mg once weekly. The product information states that 2.5 mg, 7.5 mg and 12.5 mg once weekly are not maintenance doses as they were only used for 4 weeks to escalate to the recommended dose in the trial program.

4.6 The ESC noted that a recent sponsor-commissioned analysis of tirzepatide treatment patterns for type 2 diabetes was identified during the evaluation (Mody 2025). The analysis was based on a retrospective analysis of insurance claims data from the United States between May 2022 and January 2023. The ESC noted the analysis suggested that many patients will be managed with lower tirzepatide dose strengths with 5 mg tirzepatide the most commonly used dose at the 6th script (Table 3). The ESC noted that tirzepatide was most commonly used in combinations with metformin (80.6%), SGLT2 inhibitors (41.6%) and insulin (27.5%).

Table 3: Tirzepatide dosing reported in sponsor-commissioned analysis of tirzepatide treatment patterns for type 2 diabetes

Tirzepatide dose strength	1st script N = 14,986	2nd script N = 13,856	3rd script N = 12,675	4th script N = 11,095	5th script N = 9,400	6th script N = 7,304
2.5 mg, n (%)	6,476 (43.2)	2,752 (19.9)	1,609 (12.7)	1,017 (9.2)	666 (7.1)	450 (6.2)
5 mg, n (%)	6,133 (40.9)	7,164 (51.7)	5,444 (43.0)	3,978 (35.8)	2,872 (30.6)	1,934 (26.5)
7.5 mg, n (%)	1,236 (8.2)	2,206 (15.9)	2,941 (23.2)	2,614 (23.6)	2,211 (23.5)	1,743 (23.9)
10 mg, n (%)	737 (4.9)	1,064 (7.7)	1,664 (13.1)	1,981 (17.8)	1,808 (19.2)	1,473 (20.2)
12.5 mg, n (%)	203 (1.4)	367 (2.6)	560 (4.4)	848 (7.6)	1,003 (10.7)	805 (11.0)
15 mg, n (%)	201 (1.3)	303 (2.2)	457 (3.6)	657 (5.9)	840 (8.9)	899 (12.3)

Source: Figure 2 of the Mody 2025 publication

4.7 The previous tirzepatide submissions requested PBS listings for multiple presentations (single-use pre-filled pens, single-use vials and multi-dose pre-filled pens) to ensure that the potential high demand for this treatment was met. However, the current resubmission only requested listing for the multi-dose pre-filled pens as the sponsor is confident in the supply of this presentation of tirzepatide.

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

5 Comparator

5.1 The resubmission nominated semaglutide as the main comparator. The PBAC previously considered that this was appropriate (para 7.5, tirzepatide PSD, November 2024 PBAC meeting).

5.2 The resubmission argued that the most appropriate comparisons were between tirzepatide 10 mg (or 15 mg once weekly for patients who want to maximise clinical benefit) and semaglutide 1 mg once weekly, as well as between tirzepatide 5 mg and semaglutide 0.5 mg once weekly. To support this argument the resubmission noted that the majority of semaglutide scripts were for the 1 mg dose strength suggesting that patients will titrate to the maximum tolerated dose to maximise clinical benefits (semaglutide PBS scripts in 2024, 0.5 mg: 17.7%; 1 mg: 82.3%). The resubmission stated that expert advice from general practitioners and endocrinologists also suggests that clinicians would aim to escalate to the highest possible dose of tirzepatide to maximise clinical benefits.

5.3 Market research presented in the resubmission indicated that the expected distribution of tirzepatide maintenance doses from general practitioners was 5 mg: [redacted]%, 10 mg: [redacted]%, 15 mg: [redacted]% and for endocrinologists was 5 mg: [redacted]%, 10 mg: [redacted]%, 15 mg: [redacted]%. The ESC considered that these estimates were not consistent with the claim that tirzepatide 5 mg should be considered as a titration dose. In addition, the ESC considered that the sponsor-commissioned work using prescribing data from the United States (see paragraph 4.6) indicated that tirzepatide 5 mg was the most commonly used strength.

5.4 The PBAC has not previously accepted the claim that tirzepatide 5 mg is a temporary dose. The PBAC previously stated that the comparison of tirzepatide 5 mg and semaglutide 1 mg once weekly was informative given the increased adverse events associated with higher doses of tirzepatide may limit titration to higher doses in

practice; and the requested price for tirzepatide 5 mg was higher than semaglutide 1 mg (para 7.6, tirzepatide PSD, November 2024 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. In addition to reiterating points made in the pre-PBAC response (see paragraphs 6.92 and 6.93) the sponsor answered questions from the Committee regarding use of tirzepatide in combination with insulin and the dose titration process for this drug.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (115), health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted that 77 of the 95 individuals who reported they have used this medicine for their own health condition did not indicate they had type 2 diabetes but instead provided input that focused on a PBS listing for weight loss. Input from individuals who reported they have used this medicine for type 2 diabetes described the benefits of tirzepatide use including improved daily blood glucose readings, improved HbA1c results and weight loss. Reductions in insulin requirements and the need for other diabetes medications were also reported by some individuals who had used this medicine. Improvements in quality of life were noted by one individual. The cost of tirzepatide was noted as an access and equity issue. One individual reported needing to ration medication or go without it due to cost. The PBAC noted that 11 of the 19 individuals who would like to access tirzepatide to treat their own health condition but had not used the medicine provided input that focused on a PBS listing for weight loss, and did not indicate they had type 2 diabetes. Input from individuals who would like to use tirzepatide to treat type 2 diabetes indicated that they had not done so to date due to cost considerations. The input from these individuals described how current treatment options have not been effective at controlling blood sugar levels or how they had experienced side effects from the treatments they had tried. The PBAC noted that input from a person directly caring for an individual with type 2 diabetes reported that semaglutide has been used effectively for the persons condition but noted that supply of this agent had been an issue. The PBAC noted that the input received from individuals that focused on a PBS listing of tirzepatide for weight loss would be fed into 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 Aged Care on equitable access to pharmacotherapies to treat obesity.[1]

6.3 The PBAC noted that the input received from health care professionals described the effectiveness of GLP-1 analogues in type 2 diabetes and the potential for additional benefits with the dual GLP-1/GIP actions of tirzepatide. The burden of type 2 diabetes in Aboriginal and Torres Strait Islander peoples was also highlighted. The concerns raised by individuals around the cost of tirzepatide as a barrier to access were reiterated by health care professionals. The potential for use outside of the proposed type 2 diabetes indication was also raised as a concern by a health care professional.

6.4 Comments from National Aboriginal Community Controlled Health Organisation (NACCHO) highlighted the impact of type 2 diabetes on its community, noting that almost one in six (15.5%) Aboriginal and Torres Strait Islander adults have diabetes.[2] Indigenous Australians were 2.9 times as likely to be living with the condition as non-Indigenous Australians[3] and are more likely to die from the condition. The input described research from New Zealand that reported that ethnic groups disproportionately affected by type 2 diabetes (Māori, Pacific peoples, Indian) were more likely to discontinue metformin than other ethnic groups and more likely to reinitiate treatment following discontinuation.[4] The input indicated this reflects a cyclical pattern of use where there can be prioritisation of immediate health effects over potential long-term benefits. The input went on to describe ACCHO health promotion activities where patients turn up at clinics each week for their GLP1 injections, weigh in, share a healthy lunch and often collect a blister pack of other oral diabetes and chronic medicine disease medications at the same time. The input described how patients report improvements in mental health and see the injections as a way of taking back control of their health. NACCHO acknowledged the potential costs associated with a large volume of people using this medicine but suggested that optimal use may generate downstream savings for the health system.

6.5 Comments from the Diabetes Alliance highlighted the impact of type 2 diabetes in Australia noting that over 1.3 million people with this condition are registered on the

[1] 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

[2] Australian Bureau of Statistics. (2022-24). National Aboriginal and Torres Strait Islander Health Measures Survey. ABS. https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/national-aboriginal-and-torres-strait-islander-health-measures-survey/2022-24.

[3] Australian Institute of Health and Welfare. (2024). Diabetes: Australian facts. AIHW. https://www.aihw.gov.au/reports/diabetes/diabetes

[4] Horsburgh S, Sharples K, Barson D, Zeng J, Parkin L. (2021). Patterns of metformin monotherapy discontinuation and reinitiation in people with type 2 diabetes mellitus in New Zealand. PLoS ONE 16(4): e0250289. https://doi.org/10.1371/journal.pone.0250289

National Diabetes Services Scheme. Consistent with the comments from NACCHO, the disease burden experienced by Aboriginal and Torres Strait Islander peoples was noted. The physical symptoms and complications of type 2 diabetes were also noted along with the potential implications of such complications on work performance of individuals with the condition. The input noted that 'The State of Diabetes Mellitus in Australia in 2024' report highlighted the effectiveness of GLP-1 analogues and suggested that providing more widespread access would be a positive step in managing diabetes in Australia.[5]

Clinical trials

6.6 The resubmission did not present an updated literature search.

6.7 The resubmission was based on the following comparisons previously considered by the PBAC in the July 2023 submission:

- Direct comparison of tirzepatide 10 mg and 15 mg versus semaglutide 1.0 mg in patients on background metformin therapy (SURPASS-2).
- Supportive indirect comparison of tirzepatide 5 mg (SURPASS-2) versus semaglutide 0.5 mg (SUSTAIN 7) with semaglutide 1.0 mg as the common reference in patients on background metformin therapy.

6.8 The resubmission also presented a supportive comparison of tirzepatide 5 mg, 10 mg and 15 mg once weekly versus placebo in patients on background insulin glargine therapy (SURPASS-5). This study has not previously been considered by PBAC.

6.9 The resubmission did not present any data comparing tirzepatide with semaglutide when used in combination with sulfonylurea or insulin.

6.10 During the evaluation, it was noted that there is an ongoing trial comparing cardiovascular outcomes with tirzepatide (flexible titration to maximum tolerated dose) versus dulaglutide when used as monotherapy or as combination therapy with other glucose-lowering medications in overweight/obese patients with type 2 diabetes and atherosclerotic cardiovascular disease (SURPASS-CVOT, expected completion June 2025). The ESC considered that further details from the sponsor regarding timing of the results of the SURPASS-CVOT trial would be informative if available. The PBAC noted that no further details regarding the SURPASS-CVOT trial were provided in the pre-PBAC response.

6.11 Details of the trials presented in the resubmission are provided in Table 4.

[5] House of Representatives Standing Committee on Health, Aged Care and Sport. (2024). The State of Diabetes Mellitus in Australia in 2024. Parliament of Australia. https://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Inquiry_into_Diabetes/Report

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
SURPASS-2	Clinical study report (2021). A phase 3, randomized, open-label trial comparing efficacy and safety of tirzepatide versus semaglutide once weekly as add-on therapy to metformin in patients with type 2 diabetes.	Internal study report
	Frias JP, Davies M, Rosenstock J, et al (2021). Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes.	*New England Journal of Medicine*; 385:503-15
SURPASS-5	Clinical study report (2021). A randomized, phase 3, double-blind trial comparing the effect of the addition of tirzepatide versus placebo in patients with type 2 diabetes inadequately controlled on insulin glargine with or without metformin.	Internal study report
	Dahl D, Onishi Y, Norwood P, et al (2022). Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes. The SURPASS-5 randomized clinical trial.	*Journal of the American Medical Association*; 327(6):534-545
SUSTAIN 7	Pratley RE, Aroda VR, Lingvay I, et al (2018). Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial	*Lancet Diabetes & Endocrinology*; 6:275-86
	Pratley RE, Aroda VR, Catarig AM, et al (2020). Impact of patient characteristics on efficacy and safety of once-weekly semaglutide versus dulaglutide: SUSTAIN-7 *post hoc* analyses	*BMJ Open*; 10:e037883

Source: Constructed during the evaluation

6.12 The key features of the included trials are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Tirzepatide versus semaglutide						
SURPASS-2	1,878	MC, R, OL, AC 40 weeks	High	Type 2 diabetes on metformin alone	HbA1c, weight, other biomarkers, quality of life and adverse events	Patient characteristics and treatment effects
Tirzepatide versus placebo						
SURPASS-5	475	MC, R, DB, AC 40 weeks	Unclear	Type 2 diabetes on insulin glargine	HbA1c, weight, other biomarkers, quality of life and adverse events	Not used
Semaglutide versus dulaglutide						
SUSTAIN 7	1,199	MC, R, OL, AC 40 weeks	High	Type 2 diabetes on metformin alone	HbA1c, weight, other biomarkers, quality of life and adverse events	Treatment effects for semaglutide 0.5 mg

Source: Table 2.3.1, p96; Table 2.4.1, p96 of the November 2024 tirzepatide commentary; Dahl 2022 publication
Abbreviations: AC, active-control; DB, double-blind; HbA1c, glycated haemoglobin; MC, multicentre; OL, open-label; R, randomised.

6.13 The PBAC previously considered that the SURPASS-2 trial had a high risk of bias noting the open-label study design and differential discontinuations between treatment arms (para 7.6, tirzepatide PSD, July 2023 PBAC meeting).

6.14 The risk of bias in the SURPASS-5 trial was unclear given that the study authors acknowledged the potential for unblinding due to the gastrointestinal events, weight loss and improvement in glycaemic measures (patients self-monitored glucose levels) associated with tirzepatide treatment (Dahl 2022). Additionally, there were differential discontinuations between treatment arms (tirzepatide 5 mg: 9.5%;

tirzepatide 10 mg: 11.8%; tirzepatide 15 mg: 18.3%; placebo: 3.3%; p = 0.002), primarily due to adverse events in the tirzepatide treatment arms.

6.15 The trials used fixed dosing of tirzepatide and semaglutide which was inconsistent with the respective product information documents which recommend flexible titration.

6.16 Patients included in the SURPASS-2 and SUSTAIN-7 clinical trials were required to have inadequate glycaemic control despite treatment with metformin alone. This population may not be representative of patients who have not achieved a clinically meaningful response to treatment with at least one of: metformin, a sulfonylurea or insulin, and had inadequate response/intolerance/contraindication to an SGLT2 inhibitor.

6.17 The patient population in the SURPASS-5 trial was inadequately controlled using insulin glargine with or without metformin. This population is likely to be relevant to at least a subset of the target PBS population. However, as noted in previous tirzepatide submissions, there are no clinical trial data to assess the impact of adding insulin glargine to patients inadequately controlled with a GLP-1/GIP therapy, which is likely to be a common treatment sequence in clinical practice.

Comparative effectiveness

6.18 Table 6 summarises the mean change in HbA1c over time with tirzepatide and semaglutide in patients using metformin background therapy (SURPASS-2) as well as between tirzepatide and placebo in patients using insulin glargine background therapy (SURPASS-5).

Table 6: Mean change in HbA1c from baseline (treatment regimen estimand)

SURPASS-2 (metformin background therapy)				
HbA1c, %	**Tirzepatide 5 mg N = 470**	**Tirzepatide 10 mg N = 469**	**Tirzepatide 15 mg N = 469**	**Semaglutide 1 mg N = 468**
Baseline, mean (SD)	8.32 (1.08)	8.30 (1.02)	8.26 (1.00)	8.25 (1.01)
Week 40, mean (SD)	6.23 (0.98)	5.99 (0.97)	5.92 (0.97)	6.37 (0.98)
Change from baseline, LSM (SE)	-2.01 (0.04)	-2.24 (0.05)	-2.30 (0.05)	-1.86 (0.05)
Tirzepatide vs semaglutide, LSM difference (95% CI)	**-0.15 (-0.28, -0.03)**	**-0.39 (-0.51, -0.26)**	**-0.45 (-0.57, -0.32)**	-
SURPASS-5 (insulin glargine background therapy)				
HbA1c, %	**Tirzepatide 5 mg N = 116**	**Tirzepatide 10 mg N = 119**	**Tirzepatide 15 mg N = 120**	**Placebo N = 120**
Baseline, mean (SD)	8.30 (0.88)	8.36 (0.83)	8.22 (0.84)	8.38 (0.83)
Week 40, mean (SD)	6.12 (0.78)	5.88 (0.73)	5.85 (0.89)	7.47 (1.10)
Change from baseline, LSM (SE)	-2.11 (0.09)	-2.40 (0.09)	-2.34 (0.09)	-0.86 (0.08)
Tirzepatide vs placebo, LSM difference (95% CI)	**-1.24 (-1.48, -1.01)**	**-1.53 (-1.77 to -1.30)**	**-1.47 (-1.71 to -1.23)**	-

Source: Table 2.5.1, p100 of the November 2024 tirzepatide commentary; Table GPGI.8.27, pp610-611 of the SURPASS-5 trial report; Dahl 2022 publication

Abbreviations: CI, confidence interval; LSM, least squares mean; SD, standard deviation; SE, standard error

Bolded estimates indicate statistically significant results based on graphical multiple-testing results controlled for Type I error

6.19 Treatment with tirzepatide 5 mg, 10 mg and 15 mg once weekly was associated with statistically significant reductions in HbA1c from baseline to Week 40 compared with semaglutide 1 mg once weekly in patients using metformin background therapy. Numerically larger improvements were observed with tirzepatide 10 and 15 mg doses compared to the 5 mg dose. The PBAC previously considered that only the tirzepatide 10 mg and 15 mg once weekly doses had consistently demonstrated clinically important improvements in HbA1c compared to semaglutide across different statistical analyses (para 7.8, tirzepatide PSD, July 2023 PBAC meeting). Prespecified subgroup analyses presented in the SURPASS-2 trial report indicated statistically significant treatment interactions in regard to race and baseline BMI.

6.20 Treatment with tirzepatide was also associated with statistically significant reductions in HbA1c from baseline to Week 40 compared with placebo in patients using insulin glargine background therapy. Prespecified subgroup analyses presented in the SURPASS-5 trial report indicated statistically significant treatment interactions in regard to baseline HbA1c, baseline metformin use and baseline estimated glomerular filtration rate.

6.21 Table 7 summarises the mean change in body weight over time with tirzepatide and semaglutide in patients using metformin background therapy (SURPASS-2) as well as between tirzepatide and placebo in patients using insulin glargine background therapy (SURPASS-5).

Table 7: Mean change in body weight from baseline (treatment regimen estimand)

SURPASS-2 (metformin background therapy)				
Body weight, kg	**Tirzepatide 5 mg N = 470**	**Tirzepatide 10 mg N = 469**	**Tirzepatide 15 mg N = 469**	**Semaglutide 1 mg N = 468**
Baseline, mean (SD)	92.5 (21.8)	94.8 (22.7)	93.8 (21.8)	93.7 (21.1)
Week 40, mean (SD)	84.5 (21.0)	85.3 (22.3)	82.3 (20.0)	87.7 (20.4)
Change from baseline, LSM (SE)	-7.6 (0.33)	-9.3 (0.32)	-11.2 (0.32)	-5.7 (0.32)
Tirzepatide vs semaglutide, LSM difference (95% CI)	**-1.9 (-2.8, -1.0)**	**-3.6 (-4.5, -2.7)**	**-5.5 (-6.4, -4.6)**	-
SURPASS-5 (insulin glargine background therapy)				
Body weight, kg	**Tirzepatide 5 mg N = 116**	**Tirzepatide 10 mg N = 119**	**Tirzepatide 15 mg N = 120**	**Placebo N = 120**
Baseline, mean (SD)	95.8 (19.8)	94.6 (22.3)	96.0 (22.7)	94.2 (21.8)
Week 40, mean (SD)	89.9 (20.4)	87.3 (22.2)	86.8 (23.0)	95.8 (23.4)
Change from baseline, LSM (SE)	-5.4 (0.59)	-7.5 (0.58)	-8.8 (0.59)	1.6 (0.58)
Tirzepatide vs placebo, LSM difference (95% CI)	**-7.1 (-8.7, -5.4)**	**-9.1 (-10.7, -7.5)**	**-10.5 (-12.1, -8.8)**	-

Source: Table 2.5.3, p102 of the November 2024 tirzepatide commentary; Table GPGI.8.37, p658-659 of the SURPASS-5 trial report; Dahl 2022 publication

Abbreviations: CI, confidence interval; LSM, least squares mean; SD, standard deviation; SE, standard error

Bolded estimates indicate statistically significant results based on graphical multiple-testing results controlled for Type I error.

6.22 Treatment with tirzepatide 5 mg, 10 mg and 15 mg once weekly was associated with statistically significant reductions in body weight from baseline to Week 40 compared with semaglutide 1 mg once weekly in patients using metformin background therapy. The PBAC previously considered that only the tirzepatide 10 mg and 15 mg once

weekly doses achieved clinically important short-term weight loss improvements compared to semaglutide (para 7.9, tirzepatide PSD, July 2023 PBAC meeting). Prespecified subgroup analyses presented in the SURPASS-2 trial report indicated statistically significant treatment interactions in regard to age, duration of diabetes, baseline BMI, race, geographic region and ethnicity.

6.23 Treatment with tirzepatide was also associated with statistically significant reductions in body weight from baseline to Week 40 compared with placebo in patients using insulin glargine background therapy. Prespecified subgroup analyses presented in the SURPASS-5 trial report indicated statistically significant treatment interactions in regard to age, duration of diabetes and baseline HbA1c.

6.24 There were no statistically significant differences in EQ-5D visual analogue scores or EQ-5D-5L index scores between tirzepatide and semaglutide in patients using metformin background therapy. This was consistent with other patient reported outcomes and quality of life measures which showed minimal or no differences between treatment arms.

6.25 Treatment with tirzepatide 10 mg and 15 mg once weekly was associated with improvements in EQ-5D-5L scores compared to placebo in patients using insulin glargine background therapy. There were no notable differences in EQ-5D-5L scores between tirzepatide 5 mg once weekly and placebo. This was consistent with other patient reported outcomes and quality of life measures which suggested that improvements were limited to the higher dose strengths of tirzepatide.

6.26 A Bucher indirect comparison of tirzepatide (based on the SURPASS-2 trial) and semaglutide 0.5 mg (based on the SUSTAIN 7 trial) in patients using metformin background therapy indicated that all doses of tirzepatide were associated with statistically significant reductions in HbA1c and body weight compared to semaglutide 0.5 mg.

6.27 The resubmission did not present any comparisons of tirzepatide versus semaglutide when used in combination with sulfonylurea or insulin.

Comparative harms

6.28 An overall summary of the adverse events reported in the SURPASS-2 and SURPASS-5 trials is presented in Table 8.

Table 8: Summary of key adverse events in the SURPASS-2 and SURPASS-5 trials

SURPASS-2 (metformin background therapy)				
Patients, n (%)	**Tirzepatide 5 mg N = 470**	**Tirzepatide 10 mg N = 469**	**Tirzepatide 15 mg N = 470**	**Semaglutide 1 mg N = 469**
Any adverse event	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)
Treatment-related adverse event	188 (40.0)	221 (47.1)	225 (47.9)	194 (41.4)
Serious adverse event	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)
Adverse events leading to treatment discontinuation	28 (6.0)	40 (8.5)	40 (8.5)	19 (4.1)
Deaths	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)
SURPASS-5 (insulin glargine background therapy)				
Patients, n (%)	**Tirzepatide 5 mg N = 116**	**Tirzepatide 10 mg N = 119**	**Tirzepatide 15 mg N = 120**	**Placebo N = 120**
Any adverse event	85 (73.3)	81 (68.1)	94 (78.3)	81 (67.5)
Treatment-related adverse event	43 (37.1)	46 (38.7)	63 (52.5)	17 (14.2)
Serious adverse event	9 (7.8)	13 (10.9)	9 (7.5)	10 (8.3)
Adverse events leading to treatment discontinuation	7 (6.0)	10 (8.4)	13 (10.8)	3 (2.5)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	(0.0)

Source: Table 2.5.5, p105 of the November 2024 tirzepatide commentary; Table GPGI.5.21, p208 of the SURPASS-5 trial report

6.29 All doses of tirzepatide were associated with a higher incidence of serious adverse events and adverse events leading to treatment discontinuation compared to semaglutide in patients using metformin background therapy. Treatment with higher doses of tirzepatide (10 mg and 15 mg once weekly) was also associated with an increased incidence of treatment-related adverse events. The differences in adverse events between treatment arms were largely due to the increased incidence of gastrointestinal events (such as nausea, vomiting, diarrhoea) with tirzepatide treatment which occurred primarily during the dose escalation period. Treatment with tirzepatide was also associated with higher levels of concomitant antiemetic, antinauseant and antipropulsive medication use. The hypoglycaemia event rate per 100 patient years was 0.94 for tirzepatide 5 mg, 0.46 for tirzepatide 10 mg, 2.12 for tirzepatide 15 mg and 0.47 for semaglutide 1 mg (based on severe events requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose <3.0 mmol/L).

6.30 All doses of tirzepatide were associated with a substantially higher incidence of treatment-related adverse events and adverse events leading to treatment discontinuation compared to placebo in patients using insulin glargine background therapy. The differences in adverse events were primarily driven by the higher incidence of gastrointestinal events with tirzepatide treatment. The hypoglycaemia event rate per 100 patient years was 49 for tirzepatide 5 mg, 66 for tirzepatide 10 mg, 38 for tirzepatide 15 mg and 51 for placebo (based on severe events requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose <3.0 mmol/L).

Benefits/harms

6.31 A summary of comparative benefits and harms for tirzepatide versus semaglutide based on the SURPASS-2 trial population is presented in Table 9.

Table 9: Comparative benefits and harms for tirzepatide versus semaglutide 1 mg in patients

	Tirzepatide	Semaglutide	Treatment difference
Tirzepatide 5 mg versus semaglutide 1 mg			
Proportion of patients with HbA1c < 7.0% at Week 40	82.0%	79.0%	3.0%
Proportion of patients with ≥5% weight loss at Week 40	65.3%	54.0%	11.3%
Proportion of patients with ≥10% weight loss at Week 40	34.5%	23.9%	10.6%
Proportion of patients with ≥15% weight loss at Week 40	14.7%	8.0%	6.7%
Incidence of adverse events	63.6%	64.2%	-0.6%
Incidence of serious adverse events	7.0%	2.8%	4.2%
Adverse events leading to treatment discontinuation	6.0%	4.1%	1.9%
Tirzepatide 10 mg versus semaglutide 1 mg			
Proportion of patients with HbA1c < 7.0% at Week 40	85.6%	79.0%	6.6%
Proportion of patients with ≥5% weight loss at Week 40	76.2%	54.0%	22.2%
Proportion of patients with ≥10% weight loss at Week 40	46.7%	23.9%	22.8%
Proportion of patients with ≥15% weight loss at Week 40	23.9%	8.0%	15.9%
Incidence of adverse events	68.7%	64.2%	4.5%
Incidence of serious adverse events	5.3%	2.8%	2.5%
Adverse events leading to treatment discontinuation	8.5%	4.1%	4.4%
Tirzepatide 15 mg versus semaglutide 1 mg			
Proportion of patients with HbA1c <7.0% at Week 40	86.2%	79.0%	7.2%
Proportion of patients with ≥5% weight loss at Week 40	79.7%	54.0%	25.7%
Proportion of patients with ≥10% weight loss at Week 40	56.9%	23.9%	33.0%
Proportion of patients with ≥15% weight loss at Week 40	35.8%	8.0%	27.8%
Incidence of adverse events	68.9%	64.2%	4.7%
Incidence of serious adverse events	5.7%	2.8%	2.9%
Adverse events leading to treatment discontinuation	8.5%	4.1%	4.4%

Source: Table 2.5.2, p100, Table 2.5-4, p103; Table 2.5.5, p105 of the November 2024 tirzepatide commentary

6.32 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 5 mg in comparison with semaglutide 1 mg over 40 weeks:

- 3 additional patients would achieve a glycaemic target <7.0%.
- 11 additional patients would experience ≥5% weight loss, 11 additional patients would experience ≥10% weight loss and 7 additional patients would experience ≥15% weight loss from baseline.
- There would be no apparent differences in generic quality of life measures and minimal differences in disease-specific quality of life measures and patient-reported outcomes.
- There would be 4 additional patients with serious adverse events and 2 additional patients with adverse events leading to treatment discontinuation.

6.33 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 10 mg in comparison with semaglutide 1 mg over 40 weeks:

- 7 additional patients would achieve a glycaemic target <7.0%.

- 22 additional patients would experience ≥5% weight loss, 23 additional patients would experience ≥10% weight loss and 16 additional patients would experience ≥15% weight loss from baseline.
- There would be no apparent differences in generic quality of life measures and minimal differences in disease-specific quality of life measures and patient-reported outcomes.
- There would be 3 additional patients with serious adverse events and 4 additional patients with adverse events leading to treatment discontinuation.

6.34 Based on the SURPASS-2 trial, for every 100 type 2 diabetes patients treated with tirzepatide 15 mg in comparison with semaglutide 1 mg over 40 weeks:

- 7 additional patients would achieve a glycaemic target <7.0%.
- 26 additional patients would experience ≥5% weight loss, 33 additional patients would experience ≥10% weight loss and 28 additional patients would experience ≥15% weight loss from baseline.
- There would be no apparent differences in generic quality of life measures and minimal differences in disease-specific quality of life measures and patient-reported outcomes.
- There would be 3 additional patients with serious adverse events and 4 additional patients with adverse events leading to treatment discontinuation.

6.35 The resubmission did not present sufficient clinical data to assess the benefits/harms of tirzepatide compared to semaglutide in patients using sulfonylurea or insulin background therapy.

Clinical claim

6.36 The resubmission described tirzepatide 5 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to semaglutide 0.5 mg once weekly in patients using metformin background therapy. The PBAC has previously considered that this claim was reasonable for efficacy but not safety (para 6.57 and 7.10, tirzepatide PSD, July 2023 PBAC meeting).

6.37 The resubmission did not make a clinical claim between tirzepatide 5 mg once weekly and semaglutide 1 mg once weekly in patients using metformin background therapy. However, the PBAC previously considered that the available data did not support superior efficacy and non-inferior safety of tirzepatide 5 mg versus semaglutide 1 mg (para 7.10 and 7.11, tirzepatide PSD, July 2023 PBAC meeting). With no change in the clinical evidence, the ESC considered the advice provided by the PBAC in July 2023 for the tirzepatide 5 mg comparison remained appropriate for this resubmission.

6.38 The resubmission described tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly as superior in terms of efficacy and non-inferior in terms of safety compared to semaglutide 1 mg once weekly in patients using metformin background therapy. The PBAC has previously considered that this claim was reasonable for efficacy but not safety (para 7.10 and 7.11, tirzepatide PSD, July 2023 PBAC meeting).

The ESC considered the July 2023 PBAC advice regarding the clinical claims for the tirzepatide 10 mg and tirzepatide 15 mg doses remained appropriate for this resubmission.

6.39 The resubmission did not make any clinical claims regarding the comparative efficacy and safety of tirzepatide and semaglutide in patients using sulfonylurea or insulin background therapy.

6.40 The PBAC reaffirmed its previous advice that the claim of superior comparative effectiveness was reasonable for tirzepatide 5 mg once weekly compared to semaglutide 0.5 mg once weekly and for tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly compared to semaglutide 1 mg once weekly. In addition, the PBAC reaffirmed its previous advice that the comparison of tirzepatide 5 mg and semaglutide 1 mg remained relevant, but this comparison did not support a clinically meaningful difference.

6.41 The PBAC reaffirmed its previous advice that the claim of non-inferior comparative safety was not adequately supported by the data for any of the comparisons.

Economic analysis

6.42 The resubmission presented a modelled economic evaluation of tirzepatide 10 mg and 15 mg once weekly compared to semaglutide 1 mg once weekly in patients using metformin background therapy based on clinical data from the SURPASS-2 trial with additional modelled data.

6.43 The resubmission also presented a scenario analysis comparing tirzepatide 5 mg once weekly with semaglutide 0.5 mg once weekly in patients using metformin background therapy based on an indirect comparison of the SURPASS-2 and SUSTAIN-7 trials with additional modelled data. The comparison of tirzepatide 5 mg once weekly with semaglutide 0.5 mg once weekly was considered as a supportive analysis and was not presented.

6.44 The PBAC previously indicated that the comparative cost-effectiveness of tirzepatide 5 mg once weekly compared to semaglutide 1 mg once weekly was also relevant given the increased adverse events associated with higher doses of tirzepatide may limit titration to higher doses in practice; and the requested price for tirzepatide 5 mg was higher than semaglutide 1 mg (para 7.6, tirzepatide PSD, November 2024 PBAC meeting). Therefore, a comparison of the cost-effectiveness of tirzepatide 5 mg versus semaglutide 1 mg once weekly was also conducted during the evaluation. The ESC considered that prescribing data from the United States (see paragraph 4.6) indicated that tirzepatide 5 mg was widely used and remained important.

6.45 The resubmission presented a sensitivity analysis that assumed that patients may remain on GLP-1/GIP therapy after insulin intensification and would retain the same relative treatment effects as observed in patients using metformin background therapy. However, the resubmission provided no evidence on the comparative efficacy and safety of tirzepatide and semaglutide in patients using background

therapy with insulin or a sulfonylurea. Therefore, the comparative cost-effectiveness of these treatments in the broader population remains unclear.

6.46 The main changes to the current economic model compared to the November 2024 economic model were the change in modelled patient population and treatment effects (previously based on SURPASS-2 obese subgroup data now based on SURPASS-2 overall population data), an increase in the insulin intensification threshold (from HbA1c >7% to >8%) and a reduction in the proposed effective price of tirzepatide (approximately [redacted]% price reduction).

6.47 Table 10 summarises the key components of the economic evaluation.

Table 10: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Outcomes	Life years, quality-adjusted life years
Time horizon	Lifetime (maximum 50 years); with 1 year cycle length (no half-cycle correction)
Treatments	Tirzepatide 10 mg or 15 mg once weekly or semaglutide 1 mg once weekly in combination with metformin; with 2 further lines of insulin intensification therapy (basal insulin, basal and bolus insulin)
Methods used to generate results	Patient-level microsimulation model (10,000 patients; runtime approximately 1 hour)
Model structure	The model tracks individual patient-level changes in surrogate biomarkers over time. The risk of events in each annual cycle is determined by a randomly ordered sequence of risk modules for diabetes complications (congestive heart failure, ischaemic heart disease, first and subsequent myocardial infarction, first and subsequent stroke, blindness, ulcer, first and subsequent amputation, renal failure). Adverse event risk modules are also used to capture treatment-specific event rates for hypoglycaemia and nausea. The risk of death is captured in separate risk modules depending on patient event history (years with no event history or events, first year of events, years with history of events but no events, subsequent years of events).
Patient characteristics and circumstances of use	Baseline age, sex, race, smoking status, duration of diabetes, HbA1c, systolic blood pressure, LDL, HDL, BMI, eGFR, heart rate, white blood cell counts, haemoglobin levels and prior history of complications (albuminuria, peripheral vascular disease, atrial fibrillation, congestive heart failure, ischaemic heart disease, myocardial infarction, stroke, blindness, ulcer, amputation and renal disease) were estimated based on the SURPASS-2 whole trial population. The resubmission sampled the baseline characteristics of modelled patients assuming a normal distribution around mean values. The modelled circumstances of use assumed flat dosing of GLP-1/GIP therapies, assumed that patients would not prematurely discontinue therapy, assumed patients would switch to insulin when HbA1c >8.0% and would intensify treatment if the same threshold was reached again, assumed GLP-1/GIP therapy must be stopped with the initiation of insulin, and assumed flat dosing of insulin therapies.
Transition probabilities	Treatment effects (on HbA1c, systolic blood pressure, LDL cholesterol, HDL cholesterol, BMI, eGFR and heart rate) for GLP-1/GIP therapy were based on the SURPASS-2 whole trial population. The submission sampled treatment effects for individual modelled patients assuming a normal distribution around mean values. HbA1c, LDL cholesterol, HDL cholesterol, eGFR, WBC count, and haemoglobin were assumed to gradually progress over time, based on the UKPDS OM2 risk equations; while BMI, SBP and heart rate were assumed to remain constant while using a GLP-1/GIP therapy. No modelled patients were allowed to discontinue prematurely. Patients were assumed to intensify therapy with insulin when HbA1c >8.0%. Patients were assumed to discontinue GLP-1/GIP therapy after insulin initiation with no impact on HbA1c levels. Insulin treatment effects on HbA1c (basal insulin, basal and bolus insulin) and BMI (basal and bolus insulin only) were estimated based on a systematic review of insulin studies (Willis 2017). Other biomarkers were assumed to revert to baseline values. HbA1c, LDL cholesterol, HDL cholesterol, eGFR, WBC count,

Component	Description
	haemoglobin, BMI, SBP and heart rate were assumed to gradually progress over time, based on the UKPDS OM2 risk equations. No modelled patients were allowed to discontinue prematurely. Adverse event risk for GLP-1/GIP therapy was estimated based on the SURPASS-2 whole trial population. Adverse event risk for insulin was estimated based on the ReFLECT observational study (Fadini 2019). The risk of diabetes complications was based on the UKPDS OM2 risk equations. The risk of death was based on UKPDS OM2 risk equations for 'first year of events' and 'subsequent years of events'; and Australian 2021-2023 life tables for 'years with no event history or events' and 'years with history of events but no events'.
Utility values	The baseline utility values and disutility values for congestive heart failure, ischaemic heart disease, myocardial infarction, stroke, amputation and blindness were estimated based on the UKPDS study (Clarke 2002). The disutility values for ulcer and renal failure were estimated based on the CODE-2 study (Bagust and Beale, 2005). Age based disutility values were estimated based on an Australian general population sample (Clemens 2014). Hypoglycaemia disutility values (Evans 2013), nausea disutility values (Matza 2007) and first year weight loss utility values (Boye 2022) were estimated from published vignette studies. Weight disutility values in subsequent years were estimated based on the CODE-2 study (Bagust and Beale, 2005) and applied to all patients with a BMI >25 kg/m^2.
Costs	The cost of tirzepatide was based on fixed dosing at 5, 10 or 15 mg per week; and revised tiered effective DPMQs for each dose strength. The cost of semaglutide was based on fixed dosing of 1 mg per week and the effective DPMQ (as this was known to the sponsor). The costs of metformin, insulin glargine and insulin aspart were based on WHO defined daily doses and updated published DPMQs (no special pricing arrangements apply). The resubmission assumed that there were no additional costs associated with the management of nausea or hypoglycaemia. The resubmission estimated the updated cost of insulin administration based on the advertised price of consumables (blood glucose testing strips, injection needles and lancets) from the Diabetes Shop website (https://diabetesshop.com). The resubmission assumed that second-line therapy with basal insulin would require one injection and finger prick test per day while third-line therapy with basal and bolus insulin would require four injections and finger prick tests per day. Diabetes complications costs were primarily based on panel data from Western Australia using linked administrative claims databases (Clarke 2008). The resubmission inflated costs using the CPI Medical and hospital services index.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: 'A6.1_Tirzepatide Section 3 Model' Excel workbook provided with the resubmission.
Abbreviations: BMI, body mass index; CPI, consumer price index; DPMQ, dispensed price for maximum quantity; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; UKPDS (OM2), United Kingdom Prospective Diabetes Study (Outcomes Model 2); WHO, World Health Organization

6.48 In the model, a set of baseline characteristics (demographics, biomarkers, history of complications) is individually generated for each modelled patient. The model incorporates treatment effects for each therapy based on changes to HbA1c, systolic blood pressure, LDL cholesterol, HDL cholesterol, body mass index, estimated glomerular filtration rate and heart rate.

6.49 Most biomarkers were assumed to progress over time with the exception of BMI, systolic blood pressure and heart rate which were assumed to remain constant while

patients are receiving GLP-1/GIP therapy. The ESC noted that this was not consistent with previous PBAC advice which recommended that the model include drift for all biomarkers (para 6.93, 7.12 and 7.13; tirzepatide PSD, November 2024 PBAC meeting).

6.50 While receiving treatment, patients are at risk of experiencing nausea (GLP-1/GIP therapies for the first year only) and hypoglycaemia episodes.

6.51 During each cycle, patients may experience one or more diabetes complications (congestive heart failure, ischaemic heart disease, myocardial infarction, stroke, blindness, ulcer, amputation, renal failure) or remain event-free. Patients may experience death in any cycle. The risks of diabetes complications and mortality vary over time based on current biomarkers, demographic characteristics and prior event history.

6.52 The modelled circumstances of use were based on the following assumptions:

- Flat dosing of both tirzepatide (5 mg, 10 mg, 15 mg weekly) and semaglutide (1 mg weekly). This assumption was consistent with the trial data but was unlikely to reflect use in clinical practice as the product information documents for both treatments recommend flexible dose titration.
- Patients cannot prematurely discontinue therapy. This assumption was inconsistent with the SURPASS-2 trial data which indicated that 8.3% of tirzepatide 5 mg, 12.4% of tirzepatide 10 mg, 13.2% of tirzepatide 15 mg and 8.7% of semaglutide 1 mg patients discontinued therapy over the 40-week trial duration. In clinical practice, patients will discontinue therapy for a variety of reasons.
- Patients switch to insulin therapy if HbA1c levels exceed the treatment target of 8.0%. The nominated insulin intensification threshold was consistent with previous PBAC advice (para 6.93 and 7.17, tirzepatide PSD, November 2024 PBAC meeting). The ESC noted that in the economic model the average time to insulin initiation was 4.6 years for semaglutide and up to 5.2 years for tirzepatide 15 mg.
- The base case analysis assumed that patients must stop tirzepatide and semaglutide before switching to insulin therapy. However, the resubmission also presented a sensitivity analysis allowing GLP-1/GIP therapies to be continued after insulin initiation. This analysis assumed that all patients would be 100% persistent with all therapies, the use of concomitant GLP-1/GIP therapies would not affect insulin dose and switching to insulin would not affect the relative treatment effects of GLP-1/GIP therapies. None of these assumptions were adequately justified.
- Flat dosing of insulin therapies (basal insulin 40 IU/day; basal with bolus insulin 80 IU/day). This assumption was not consistent with use of insulin in clinical practice as therapy is typically titrated over time to maintain glycaemic control.

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

Table 11: Key drivers of the model

Description	Method/Value	Impact
Biomarker drift	The base case analysis assumed that HbA1c, LDL cholesterol, HDL cholesterol, eGFR, WBC count, and haemoglobin would gradually progress over time based on the UKPDS OM2 risk equations. BMI, SBP and heart rate were assumed to remain	Moderate, favours tirzepatide

Description	Method/Value	Impact
	constant while using a GLP-1/GIP therapy but were assumed to progress while using insulin. This approach was previously proposed in the sponsor's pre-PBAC response to the November 2024 submission which the PBAC stated was inadequate and did not refute the preferred option from ESC which was to include biomarker drift for all variables (para 6.93, 7.12 and 7.13; tirzepatide PSD, November 2024 PBAC meeting). The ESC considered its November 2024 advice to include biomarker drift for all variables remained appropriate for the resubmission and noted that this was explored in sensitivity analyses presented by the evaluation.	
Combination with insulin	The base case analysis assumed that patients must stop tirzepatide and semaglutide before switching to insulin therapy. However, a sensitivity analysis was presented that allowed GLP-1/GIP therapies to be continued after insulin initiation. The resubmission provided no evidence on the comparative efficacy and safety of tirzepatide and semaglutide in combination with insulin. The ESC noted that the sensitivity analysis assumed that all patients would be 100% persistent with all therapies, the use of concomitant GLP-1/GIP therapies would not affect insulin dose and switching to insulin would not affect the relative treatment effects of GLP-1/GIP therapies. None of these assumptions were adequately justified.	High, favours tirzepatide
Utility values	The base case analysis estimated utility/disutility values from a variety of different published sources: baseline utility (Clarke 2002), age (Clemens 2014), first year weight loss (Boye 2022), subsequent year weight (Bagust and Beale 2005), nausea (Matza 2007), hypoglycaemia (Evans 2013), diabetes complications (Clarke 2002; Bagust and Beale 2005). The ESC previously suggested testing the replacement of baseline utility, BMI, nausea and hypoglycaemia while on first-line therapy with the SUPRPASS-2 estimates to account for potential double counting (para 6.93, tirzepatide PSD, November 2024 PBAC meeting). This was not addressed in the resubmission. The ESC did not accept the PSCR argument that the vignette-based approach taken to estimate utility values was more appropriate than the use of the SURPASS-2 utility values. The ESC reaffirmed its November 2024 advice that incorporation of the SURPASS-2 trial utility values while on first-line therapy would be informative and noted that this was explored in sensitivity analyses presented by the evaluation. The model remains highly sensitive to weight-related utility values in subsequent years. Given the substantial uncertainty associated with published estimates, validation of these estimates with additional analyses of the SURPASS-2 trial assessing the relationship between change in BMI and change in utility values would be informative.	Moderate, favours tirzepatide
Hypoglycaemia events	The resubmission estimated hypoglycaemia event rates associated with insulin treatment (both second and third-line therapy) based on a multinational, observational study of diabetes patients switching from existing insulin therapies to insulin degludec between March 2015 and March 2018 (Fadini 2019). The applicability of this study to the modelled population was unclear as the publication acknowledged that the inclusion criteria limited enrolment to patients with a pre-planned switch to insulin degludec which may have selected a population with frequent hypoglycaemia (56.6% of the type 2 diabetes population in the study were classified as hypoglycaemia-prone patients). The definition of hypoglycaemia used in this analysis (an event with or without symptoms which was either confirmed or assumed to be caused by blood glucose <3.9 mmol/L) was inconsistent with the definition used to inform event rates for tirzepatide and semaglutide (a severe	Moderate, favours tirzepatide

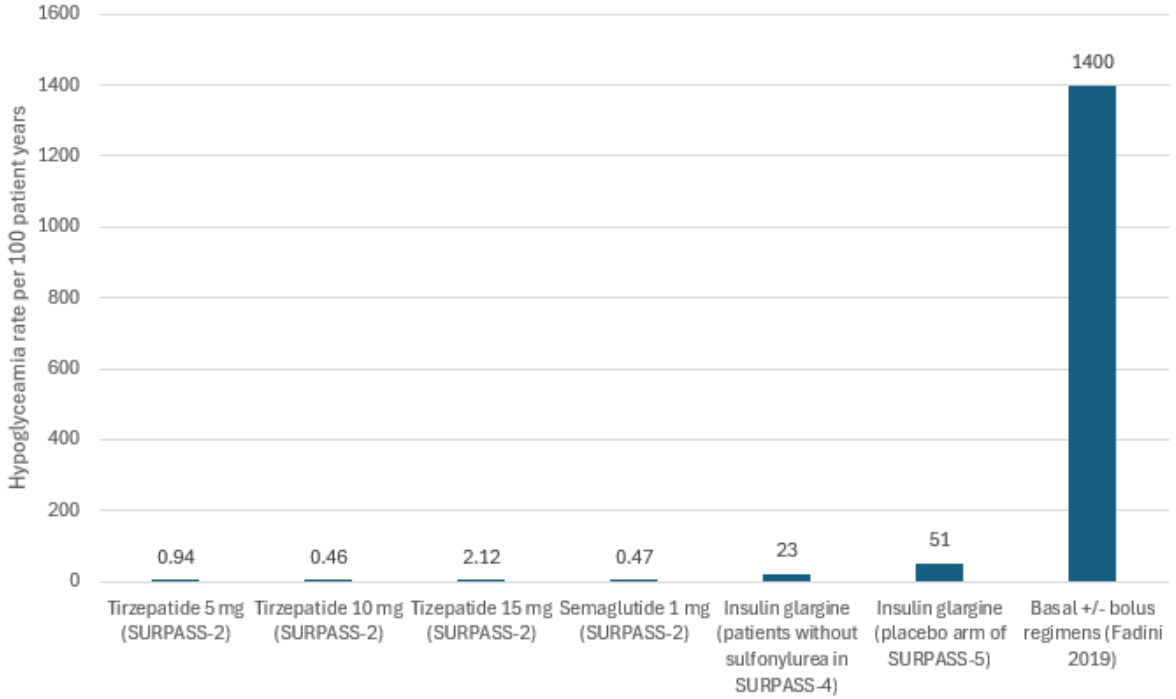
Description	Method/Value	Impact
	event requiring assistance or an event with or without symptoms which was confirmed to be caused by blood glucose <3.0 mmol/L). The ESC noted that a comparison of observed estimates from the SURPASS clinical trial program with modelled estimates based on the Fadini 2019 publication suggests that the model substantially overestimated the risk of hypoglycaemia with insulin treatment (see Figure 1 below).	

Source: Constructed during the evaluation

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESC, Economics Sub Committee; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SBP, systolic blood pressure; UKPDS OM2, United Kingdom Prospective Diabetes Study Outcomes Model 2; WBC, white blood cell.

6.54 A comparison of the observed hypoglycaemia event rates per 100 patient years with tirzepatide (SURPASS-2), semaglutide (SURPASS-2) and insulin glargine (SURPASS-4, SURPASS-5) with the modelled hypoglycaemia event rate for insulin (Fadini 2019) is presented in Figure 1.

Figure 1: Observed versus modelled hypoglycaemia event rates



Source: Table GPGL.5.30, pp276-277 of the SURPASS-2 trial report; Table GPGI.5.28, p226 of the SURPASS-5 trial report; Table S7 of the Del Prato (2021) publication; Figure 3 of the Fadini (2019) publication

6.55 The model appeared to substantially overestimate hypoglycaemia event rates with insulin compared to observed estimates from the SURPASS clinical trial program. The PSCR stated that in July 2023 and November 2024 the PBAC had advised a revised base case should incorporate a reduced hypoglycaemia disutility of 0.003 per event (para 7.16, tirzepatide PSD, July 2023 PBAC meeting; para 7.11, tirzepatide PSD, November 2024 PBAC meeting). The PSCR argued that this was to account for any uncertainty in terms of hypoglycaemic rates and hence proposed that no further changes to hypoglycaemic rates were required. The ESC agreed with the evaluation that the

hypoglycaemia rates with insulin in the economic model were substantially overestimated compared to estimates from the SURPASS clinical trial program. The ESC noted that the incremental cost effectiveness ratio is highly sensitive to this overestimate (see Table 13).

6.56 The results of the modelled economic evaluation are summarised in Table 12. During the evaluation, the modelled analyses were converted to stepped analyses in order to assess the impact of individual changes between the November 2024 base case and the current base case for each comparison.

Table 12: Results of the stepped economic evaluation from the November 2024 base case to the current model base case

	Incremental cost	Incremental QALYs	ICER
Tirzepatide 5 mg versus semaglutide 1 mg			
November 2024 base case	$[redacted]	0.0258	$[redacted][1]
Update Australian life tables to 2021-2023 values	$[redacted]	0.0259	$[redacted][1]
Change patient population from SURPASS-2 severely obese subgroup to whole trial population (impacts patient characteristics, treatment effects, age-related disutility values, nausea and weight-related disutility values)	$[redacted]	0.0273	$[redacted][1]
Increase threshold for insulin intensification to HbA1c ≥8.0%	$[redacted]	0.0369	$[redacted][2]
Adjust insulin treatment effects on HbA1c and BMI	$[redacted]	0.0310	$[redacted][3]
Allow biomarker drift for systolic blood pressure, BMI and heart rate for patients using insulin	$[redacted]	0.0317	$[redacted][3]
Decrease tirzepatide effective price and update prices for other drug and administration costs	**$[redacted]**	**0.0317**	**$[redacted][4]**
Tirzepatide 10 mg versus semaglutide 1 mg			
November 2024 base case	$[redacted]	0.0772	$[redacted][4]
Update Australian life tables to 2021-2023 values	$[redacted]	0.0773	$[redacted][4]
Change patient population from SURPASS-2 severely obese subgroup to whole trial population (impacts patient characteristics, treatment effects, age-related disutility values, nausea and weight-related disutility values)	$[redacted]	0.0645	$[redacted][5]
Increase threshold for insulin intensification to HbA1c ≥8.0%	$[redacted]	0.0862	$[redacted][5]
Adjust insulin treatment effects on HbA1c and BMI	$[redacted]	0.0815	$[redacted][6]
Allow biomarker drift for systolic blood pressure, BMI and heart rate for patients using insulin	$[redacted]	0.0821	$[redacted][6]
Decrease tirzepatide effective price and update prices for other drug and administration costs	**$[redacted]**	**0.0821**	**$[redacted][7]**
Tirzepatide 15 mg versus semaglutide 1 mg			
November 2024 base case	$[redacted]	0.1127	$[redacted][8]
Update Australian life tables to 2021-2023 values	$[redacted]	0.1128	$[redacted][8]
Change patient population from SURPASS-2 severely obese subgroup to whole trial population (impacts patient characteristics, treatment effects, age-related disutility values, nausea and weight-related disutility values)	$[redacted]	0.0826	$[redacted][5]
Increase threshold for insulin intensification to HbA1c ≥8.0%	$[redacted]	0.1132	$[redacted][6]
Adjust insulin treatment effects on HbA1c and BMI	$[redacted]	0.1066	$[redacted][6]
Allow biomarker drift for systolic blood pressure, BMI and heart rate for patients using insulin	$[redacted]	0.1072	$[redacted][6]
Decrease tirzepatide effective price and update prices for other drug and administration costs	**$[redacted]**	**0.1072**	**$[redacted][7]**

Source: 'A6.1_Tirzepatide Section 3 Model' Excel workbook provided with the resubmission.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ICER, incremental cost effectiveness ratio; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; QALY, quality adjusted life year.
Note: The estimated incremental costs, QALYs and ICERs reported for the base case in the main body of the resubmission could not replicated using the default inputs in the economic model. In the evaluation, all estimates were based on values directly from the economic model although the differences from the resubmission were minimal.
The redacted values correspond to the following ranges:
[1] *$95,000 to < $115,000*
[2] *$135,000 to < $155,000*
[3] *$155,000 to < $255,000*
[4] *$45,000 to < $55,000*
[5] *$55,000 to < $75,000*
[6] *$75,000 to < $95,000*
[7] *$25,000 to < $35,000*
[8] *$35,000 to < $45,000*

6.57 The stepped analyses assessing changes from the previous November 2024 model to the current model indicated that the change in the modelled population (whole trial population versus severely obese subgroup), the higher insulin intensification threshold (HbA1c >8% versus HbA1c >7%) and the lower proposed effective price for tirzepatide in the current resubmission (approximately [redacted]% price reduction) had the largest impacts on cost-effectiveness estimates.

6.58 Based on the economic model, treatment with tirzepatide was associated with an incremental cost per QALY gained of $45,000 to < $55,000 for the 5 mg dose, $25,000 to < $35,000 for the 10 mg dose and $25,000 to < $35,000 for the 15 mg dose compared to semaglutide 1 mg weekly. The PBAC previously considered that an incremental cost effectiveness ratio in the order of $30,000 per QALY gained would be appropriate (para 7.13, tirzepatide PSD, November 2024 PBAC meeting).

6.59 For patients treated with tirzepatide 5 mg versus semaglutide 1 mg once weekly and followed up for 50 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- Decreased incidence of diabetes complications (23 fewer non-fatal events per 10,000 patients) and an increase in survival (average gain of 5 days per patient).
- Decreased incidence of patients with nausea in the first year (50 fewer patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0190 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 3 months per patient) with a reduced incidence of hypoglycaemia events (3 fewer events per patient).
- Additional drug and administration costs of $[redacted] per person and increased diabetes complications costs of $53 per person.

6.60 For patients treated with tirzepatide 10 mg versus semaglutide 1 mg once weekly and followed up for 50 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- Decreased incidence of diabetes complications (65 fewer non-fatal events per 10,000 patients) and an increase in survival (average gain of 17 days per patient).
- Increased incidence of patients with nausea in the first year (130 additional patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0476 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 6 months per patient) with a reduced incidence of hypoglycaemia events (7 fewer events per patient).
- Additional drug and administration costs of $[redacted] per person but decreased diabetes complications costs of $219 per person.

6.61 For patients treated with tirzepatide 15 mg versus semaglutide 1 mg once weekly and followed up for 50 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- Decreased incidence of diabetes complications (84 fewer non-fatal events per 10,000 patients) and an increase in survival (average gain of 20 days per patient).
- Increased incidence of patients with nausea in the first year (420 additional patients per 10,000 patients).
- Improved quality of life associated with a temporary reduction in weight (average increase of 0.0689 quality-adjusted life years per patient).
- Delayed time to insulin therapy (average 7 months per patient) with a reduced incidence of hypoglycaemia events (8 fewer events per patient).
- Additional drug and administration costs of $[redacted] per person but decreased diabetes complications costs of $381 per person.

6.62 The PSCR continued to argue that the comparative cost-effectiveness of tirzepatide 5 mg once weekly compared to semaglutide 1 mg once weekly was not relevant. The PSCR stated that the sponsor would not accept parity pricing of tirzepatide 5 mg to semaglutide 1 mg and proposed two alternative pricing proposals for the 5 mg strength. In the first, the cost-effective price for tirzepatide 5 mg was weighted between the comparison with semaglutide 0.5 mg ([redacted]% based on expert opinion on the proportion of patients who would use tirzepatide 5 mg as a temporary titration dose) and semaglutide 1.0 mg ([redacted]% based on expert opinion on the proportion of patients who would use tirzepatide 5 mg as a maintenance dose) and resulted in a weighted effective DPMQ of $[redacted]. The second approach proposed a flat effective price across all dose strengths based on the estimated cost-effective price for tirzepatide 10 mg once weekly (effective DPMQ $[redacted]) based on the rationale that this strength is the published WHO Defined Daily Dose (DDD) for this drug. The ESC reiterated previous PBAC advice that the comparative cost-effectiveness of tirzepatide 5 mg once weekly with semaglutide 1 mg once weekly remained relevant (see paragraph 6.44). The ESC noted that both approaches proposed resulted in a DPMQ for tirzepatide 5 mg that was higher than that proposed in the resubmission (i.e. DPMQ $[redacted]). The ESC noted that using the second approach the price increase in tirzepatide 5 mg was of a similar magnitude to the price decrease for tirzepatide 15 mg (i.e. tirzepatide 15 mg DPMQ reduced from $[redacted] to $[redacted]).

6.63 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 13.

Table 13: Results of key sensitivity analyses

Analyses	ICER (% change from base case)		
	Tirzepatide 5 mg vs semaglutide 1 mg	Tirzepatide 10 mg vs semaglutide 1 mg	Tirzepatide 15 mg vs semaglutide 1 mg
Base case	$[redacted][1]	$[redacted][2]	$[redacted][2]
Discount rate (base case: 5% for benefits and costs)			
3.5% discount rate	$[redacted][1] (+[redacted]%)	$[redacted][2] (-[redacted]%)	$[redacted][2] (-[redacted]%)
0% discount rate	$[redacted][1] (+[redacted]%)	$[redacted][2] (-[redacted]%)	$[redacted][2] (-[redacted]%)
Biomarker drift (base case: biomarker drift based on UKPDS OM2 equations for HbA1c, LDL cholesterol, HDL cholesterol, eGFR, WBC count, haemoglobin; no biomarker drift for BMI, SBP, heart rate while receiving GLP-1/GIP therapies)			
No drift for any biomarker other than HbA1c	$[redacted][3] (-[redacted]%)	$[redacted][2] (-[redacted]%)	$[redacted][2] (-[redacted]%)
UKPDS drift for all biomarkers	$[redacted][1] (+[redacted]%)	$[redacted][3] (+[redacted]%)	$[redacted][3] (+[redacted]%)
Insulin treatment (base case: insulin intensification steps when HbA1c >8.0%; tirzepatide/semaglutide stopped at insulin initiation; insulin treatment effects for HbA1c and BMI based on Willis 2017; hypoglycaemia rates based on Fadini 2019)			
Assume tirzepatide/semaglutide treatment continued after insulin initiation (no reversion to baseline, insulin effects applied in addition to GLP-1/GIP, GLP-1/GIP costs maintained for duration of model) [corrected for error in drug costs in the resubmission[a]]	$[redacted][4] (+[redacted]%)	$[redacted][1] (+[redacted]%)	$[redacted][1] (+[redacted]%)
Reduce insulin hypoglycaemia rate to 23 per 100 patient years (based on the SURPASS-4 trial) but increase hypoglycaemia disutility to -0.005 per event (average disutility for non-severe daytime event in type 2 diabetes patients, Evans 2013)	$[redacted][4] (+[redacted]%)	$[redacted][3] (+[redacted]%)	$[redacted][3] (+[redacted]%)
Utility values (base case: diabetes complication disutility values primarily based on Clarke 2002; age disutility values based on Clemens 2014; nausea disutility based on Matza 2007; hypoglycaemia disutility (0.003) based on Evans 2013; first year weight loss utility values based on Boye 2022; subsequent year weight disutility values based on Bagust and Beale 2005)			
Replace baseline utility, weight loss, nausea and hypoglycaemia utilities while on first-line therapy with utility estimates from the SURPASS-2 whole trial population	$[redacted][1] (-[redacted]%)	$[redacted][2] (+[redacted]%)	$[redacted][3] (+[redacted]%)
Subsequent weight disutility based on Soltoft 2009 (+0.0171 increase per 1 BMI unit decrease)	$[redacted][4] (+[redacted]%)	$[redacted][3] (+[redacted]%)	$[redacted][1] (+[redacted]%)
Subsequent weight disutility based on Lane 2014 (-0.0472 decrease per 1 BMI unit increase)	$[redacted][5] (-[redacted]%)	$[redacted][5] (-[redacted]%)	$[redacted][5] (-[redacted]%)

Source: 'A6.1_Tirzepatide Section 3 Model' Excel workbook provided with the resubmission.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; HDL, high density lipoprotein cholesterol; ICER, incremental cost effectiveness ratio; LDL, low density lipoprotein cholesterol; QALY, quality-adjusted life year; SBP, systolic blood pressure; UKPDS OM2, United Kingdom Prospective Diabetes Study Outcomes Model 2; WBC, white blood cell.

[a] The sensitivity analysis presented in the resubmission assessing continued use of tirzepatide/semaglutide after insulin initiation did not include the ongoing drug costs for tirzepatide and semaglutide treatment after insulin initiation.

The redacted values correspond to the following ranges:

[1] $45,000 to < $55,000

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

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

[4] $55,000 to < $75,000

[5] $5,000 to < $15,000

6.64 The results of the sensitivity analyses indicated that the model was most sensitive to biomarker drift, HbA1c and BMI treatment effects, continued use of GLP-1/GIP therapies in combination with insulin, hypoglycaemia rates associated with insulin, as well as weight-related utility values.

6.65 During the evaluation, multivariate sensitivity analyses were conducted to explore the combined impact of changes to biomarker drift (previously requested by ESC), GLP-1/GIP utility values (previously requested by ESC), insulin combination therapy (relevant to the proposed optional insulin listing) and hypoglycaemia event rate (inconsistent modelling of data compared to the SURPASS trial program). The results of key multivariate sensitivity analyses are summarised in Table 14.

Table 14: Results of multivariate sensitivity analyses

Analyses	ICER (% change from base case)		
	Tirzepatide 5 mg vs semaglutide 1 mg	Tirzepatide 10 mg vs semaglutide 1 mg	Tirzepatide 15 mg vs semaglutide 1 mg
Base case	$[redacted][1]	$[redacted][2]	$[redacted][2]
Scenario 1 (UKPDS drift for all biomarkers, assume tirzepatide/semaglutide treatment continued after insulin initiation)	$[redacted][3] (+[redacted]%)	$[redacted][1] (+[redacted]%)	$[redacted][1] (+[redacted]%)
Scenario 2 (UKPDS drift for all biomarkers, hypoglycaemia rates from SURPASS-4 with higher disutility per event)	$[redacted][3] (+[redacted]%)	$[redacted][1] (+[redacted]%)	$[redacted][1] (+[redacted]%)
Scenario 3 (UKPDS drift for all biomarkers, SURPASS-2 utility values while on first-line therapy)	$[redacted][1] (+[redacted]%)	$[redacted][4] (+[redacted]%)	$[redacted][1] (+[redacted]%)
Scenario 4 (UKPDS drift for all biomarkers, assume tirzepatide/semaglutide treatment continued after insulin initiation, hypoglycaemia rates from SURPASS-4 with higher disutility per event, SURPASS-2 utility values while on first-line therapy)	$[redacted][3] (+[redacted]%)	$[redacted][5] (+[redacted]%)	$[redacted][5] (+[redacted]%)
Scenario 5 (UKPDS drift for all biomarkers, hypoglycaemia rates from SURPASS-4 with higher disutility per event, SURPASS-2 utility values while on first-line therapy)	$[redacted][3] (+[redacted]%)	$[redacted][1] (+[redacted]%)	$[redacted][5] (+[redacted]%)

Source: 'A6.1_Tirzepatide Section 3 Model' Excel workbook provided with the resubmission.
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; UKPDS, United Kingdom Prospective Diabetes Study
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$25,000 to < $35,000*
[3] *$75,000 to < $95,000*
[4] *$35,000 to < $45,000*
[5] *$55,000 to < $75,000*

6.66 The multivariate analyses suggest that the incremental cost effectiveness ratio for tirzepatide compared to semaglutide could be substantially higher than estimated in the base case analysis based on plausible combinations of various data inputs. However, the evaluation considered these estimates remain highly uncertain given that modelled circumstances of use are unlikely to be representative of clinical practice.

6.67 The ESC advised that inclusion of UKPDS drift for all biomarkers, hypoglycaemia rates from SURPASS-4 with higher disutility per event and SURPASS-2 utility values while on first-line therapy were appropriate. The ESC noted that Scenario 4 included each of these inputs along with an assumption that tirzepatide/semaglutide treatment would continue after insulin initiation. The ESC noted that assuming both treatments would be continued after insulin intensification with the same relative benefits as observed in the without insulin population resulted in a large increase in the incremental cost effectiveness ratio (see Table 13). The ESC noted the PSCR's proposal to exclude use of tirzepatide in combination with insulin from the PBS restriction. The ESC considered that if it was deemed appropriate to exclude use of tirzepatide in combination with insulin, with such use also excluded from the economic model, then measures to address concerns regarding the risk of leakage into a less cost-effective population would be required. In addition, the ESC recalled that the PBAC had previously indicated that clinicians would want the ability to use tirzepatide in combination with a sulfonylurea and/or insulin (para 7.4, tirzepatide PSD, November 2024 PBAC meeting).

6.68 The ESC advised that, assuming tirzepatide/semaglutide treatment continuation after insulin initiation was appropriate, Scenario 4 may provide a way forward. The ESC noted the incremental cost effectiveness ratios for Scenario 4 were $75,000 to < $95,000, $55,000 to < $75,000 and $55,000 to < $75,000 per QALY gained for the 5 mg, 10 mg and 15 mg strengths of tirzepatide respectively. The ESC recalled that the PBAC had previously advised that an incremental cost effectiveness ratio in the order of $30,000 per QALY gained would be appropriate and noted that each of the Scenario 4 ratios were above this. The ESC considered that it may be appropriate to weight incremental cost effectiveness ratios based on expected use, and that based on prescribing data from the United States (see paragraph 4.6) the most commonly used strength is the 5 mg dose, including the 6th script. The ESC noted, however, that this approach incorporates a premium for the 5 mg tirzepatide dose over the 1 mg semaglutide dose for which the clinical data do not support.

6.69 The pre-PBAC response acknowledged the PBAC had previously advised that an incremental cost effectiveness ratio in the order of $30,000 per QALY gained would be appropriate. In addition, the pre-PBAC response acknowledged that price reductions would be required to achieve the target incremental cost effectiveness ratio using either the Scenario 4 or Scenario 5 multivariate analyses outlined in Table 14. However, the pre-PBAC response stated that the sponsor was unable to make further concessions on the ex-manufacturer price proposed in the resubmission. The pre-PBAC response suggested a risk sharing arrangement [redacted] (see paragraph 6.92).

6.70 The PBAC noted the price reductions required to achieve an incremental cost effectiveness ratio in the order of $30,000 per QALY gained for Scenario 5 (Table 15).

Table 15: Effective DPMQs required to achieve an ICER of $30,000 per QALY gained for Scenario 5

Analyses	Tirzepatide 5 mg vs semaglutide 1 mg	Tirzepatide 10 mg vs semaglutide 1 mg	Tirzepatide 15 mg vs semaglutide 1 mg
Base case	$[redacted][1]	$[redacted][2]	$[redacted][2]
Scenario 5 (UKPDS drift for all biomarkers, hypoglycaemia rates from SURPASS-4 with higher disutility per event, SURPASS-2 utility values while on first-line therapy)	$[redacted][3] per QALY gained	$[redacted][4] per QALY gained	$[redacted][5] per QALY gained
Effective DPMQ required to achieve an ICER of 30K per QALY gained for Scenario 5	$[redacted] ($[redacted][6] per QALY gained)	$[redacted] ($[redacted][6] per QALY gained)	$[redacted] ($[redacted][6] per QALY gained)
- Required price reduction as a percentage of proposed effective price	[redacted]% reduction (proposed was $[redacted])	[redacted]% reduction (proposed was $[redacted])	[redacted]% reduction (proposed was $[redacted])
-Percentage premium compared to semaglutide	[redacted]% premium (semaglutide $[redacted])	[redacted]% premium (semaglutide $[redacted])	[redacted]% premium (semaglutide $[redacted])

Source: 'A6.1_Tirzepatide Section 3 Model' Excel workbook provided with the resubmission.
Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; UKPDS, United Kingdom Prospective Diabetes Study
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*
[2] *$25,000 to < $35,000*
[3] *$75,000 to < $95,000*
[4] *$45,000 to < $55,000*
[5] *$55,000 to < $75,000*
[6] *$25,000 to < $35,000*

Drug cost/patient/year

6.71 The estimated drug costs per patient per year for tirzepatide are summarised in Table 16.

Table 16: Drug cost per patient per year for tirzepatide

	SURPASS-2	Economic model	Financial estimates
Dose distribution	-	-	5 mg: [redacted]% 10 mg: [redacted]% 15 mg: [redacted]%
Cost per 28 days (effective DPMQ)	-	5 mg: $[redacted] 10 mg: $[redacted] 15 mg: $[redacted]	5 mg: $[redacted] 10 mg: $[redacted] 15 mg: $[redacted]
Adherence	5 mg: 95.7% [a] 10 mg: 93.4% [a] 15 mg: 94.7% [a]	100% for all doses	93% for all doses
Cost per year [b]	-	5 mg: $[redacted] 10 mg: $[redacted] 15 mg: $[redacted]	5 mg: $[redacted] 10 mg: $[redacted] 15 mg: $[redacted]
Proportion of patients on treatment in subsequent years	Treatment discontinuation at 40 weeks: 5 mg: 8.3% 10 mg: 12.4% 15 mg: 13.2%	Year 2: 92.5% [c] Year 3: 87.9% [c] Year 4: 79.1% [c] Year 5: 64.4% [c] Year 6: 45.5% [c]	Year 2: 92.5% [c] Year 3: 87.9% [c] Year 4: 79.1% [c] Year 5: 64.4% [c] Year 6: 45.5% [c]

Source: Constructed during the evaluation using the Section 3 Model and Section 4 Model, Excel workbooks of the resubmission.
[a] Based on the proportion of patients taking at least 75% of required doses.
[b] Cost per year for persistent patients.
[c] Based on proportion of patients on treatment at the start of each year in the economic model, incorporating discontinuation due to death. Weighted estimates were calculated using the fixed dose distribution used in the budget impact analysis.

6.72 The estimated drug cost for semaglutide (0.5 or 1 mg) per patient per year is $[redacted] (based on the effective DPMQ per script of $[redacted] /28 days per script x 365.25 days per year).

6.73 The PSCR proposed alternative two alternative pricing proposals for determining the cost-effective price of tirzepatide 5 mg (see paragraph 6.62).

Estimated PBS usage & financial implications

6.74 This resubmission was considered by DUSC.

6.75 The utilisation and financial estimates in the current resubmission have been extensively revised from the November 2024 submission with updated data inputs for the broader target patient population (all patients who are contraindicated, intolerant or inadequately controlled with SGLT2 inhibitors).

6.76 The resubmission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact of listing tirzepatide on the PBS/RPBS in 3 populations:

- Prevalent patients with existing eligibility based on a prior history of GLP-1 analogue use.
- Prevalent patients with existing eligibility based on a prior history of SGLT2 use who had switched to other non GLP-1 analogue regimens.
- Newly eligible patients who are using metformin monotherapy or SGLT2 inhibitors but may switch to another therapy.

6.77 A major error was identified in the estimated scripts per patient which was corrected by the sponsor during the evaluation process (the error resulted in a cumulative

underestimate of $200 million to < $300 million to the net cost to the PBS/RPBS over 6 years). All estimates presented by the evaluation were based on these revised calculations.

6.78 The key inputs used to derive the financial implications are presented in Table 17.

Table 17: Key inputs for financial estimates

Data	Value applied and source	Comment
Treated patients		
Prevalent patients treated with GLP-1 analogues	[redacted][1]. Based on a sponsor-commissioned analysis of the 10% PBS sample. Estimates used in the resubmission were based on adults and children using various GLP-1 regimens (GLP-1 analogue monotherapy; dual therapy with metformin, sulfonylurea, insulin, DPP4 inhibitors or SGLT2 inhibitors; and triple therapy with various combinations of metformin, sulfonylurea, insulin, DPP4 inhibitors and SGLT2 inhibitors) in 2024 based on a 6-month treatment window (patients assumed to remain on treatment if gap between scripts is <6 months).	The resubmission did not justify limiting prevalence estimates to 2024, as the proposed restriction allows tirzepatide treatment in patients with <u>any</u> history of GLP-1 analogue use, not just in the current year. The range of GLP-1 regimens included in the analysis may be appropriate if tirzepatide is recommended for the broader optional listing in combination with metformin, sulfonylurea and/or insulin but is likely to overestimate the potential market for tirzepatide if combinations with insulin are not allowed. The resubmission did not adequately justify the treatment window used to estimate patient numbers. The inclusion of children was not consistent with the proposed restriction for tirzepatide. DUSC considered the potential for double counting given the range of GLP-1 regimens included in the analysis. DUSC noted patients treated in previous years but not in 2024 and patients accessing treatment on the private market were not included in this approach. DUSC noted the PSCR provided revised financial estimates which excluded children. DUSC noted the negligible impact on the financial estimates, given the approach used to derive this parameter. DUSC noted a high proportion of GLP-1s utilisation is outside of the PBS restrictions and thus encompasses utilisation that may not be cost-effective. As such, DUSC considered tirzepatide utilisation for type 2 diabetes would likely be smaller than estimated
Prevalent patients treated with SGLT2 inhibitors who switched to other therapies	[redacted][2]. Based on a sponsor-commissioned analysis of the 10% PBS sample. Estimates used in the resubmission were based on extrapolated estimates of adults and children using SGLT2 regimens who switched out to other non GLP-1 regimens in 2024 (patients who used another regimen within 6-months of their last SGLT2 script). Patients who stopped diabetes treatments after SGLT2 use (drop-off definition of 6 months) were removed from the analysis.	The resubmission did not justify limiting prevalence estimates to 2024, as the proposed restriction allows tirzepatide treatment in <u>any</u> patient who has not achieved a clinically meaningful response to SGLT2 inhibitors, not just in the current year. The resubmission did not adequately justify the drop-off definition used to estimate patient numbers. The inclusion of children was not consistent with the proposed restriction for tirzepatide. DUSC agreed with the evaluation. DUSC commented that it was unclear how the submission derived this estimate and considered the potential for double counting across months.
Incident SGLT2 inhibitor switch outs	Increasing from [redacted][3] in Year 1 to [redacted][4] in Year 6. Based on a sponsor-commissioned analysis of the 10% PBS sample.	The resubmission did not adequately address the instability in SGLT2 patient numbers over time (i.e. older utilisation data fitted to a linear function may not be representative of current use) or the appropriateness of using historical data to inform

Data	Value applied and source	Comment
	Estimates used in the resubmission were based on adults and children using SGLT2 regimens who switched out to other non GLP-1 regimens between June 2018 and September 2022 (patients who used another regimen within 6-months of their last SGLT2 script). The resubmission argued that data was only used up to September 2022 due to instability in patient numbers beyond this time point. Monthly estimates were extrapolated over time using a linear function. Patients who stopped diabetes treatments after SGLT2 use (drop-off definition of 6 months) were removed from the analysis.	future estimates given the changing market dynamics of both SGLT2 inhibitors and GLP-1 analogues. The resubmission did not adequately justify the drop-off definition used to estimate patient numbers. The inclusion of children was not consistent with the proposed restriction for tirzepatide. DUSC agreed with the evaluation and considered the SGLT2 market to be unstable. DUSC considered this population was already captured as part of the prevalent population.
Incident metformin monotherapy switch outs	Increasing from [redacted][5] in Year 1 to [redacted][5] in Year 6. Based on a sponsor-commissioned analysis of the 10% PBS sample. Estimates used in the resubmission were based on adults and children using metformin monotherapy who switched out to other non GLP-1 regimens between June 2018 and September 2022 (patients who used another regimen within 6-months of their last metformin monotherapy script). The resubmission argued that data was only used up to September 2022 due to instability in patient numbers beyond this time point. Monthly estimates were extrapolated over time using a linear function. Patients who stopped diabetes treatments after metformin use (drop-off definition of 6 months) were removed from the analysis.	The resubmission did not adequately address the reliability of metformin monotherapy patient numbers as the DPMQ for metformin is lower than the general patient copayment and private use of metformin is not captured in the 10% PBS sample. The resubmission did not adequately address the instability in metformin patient numbers over time (i.e. older utilisation data fitted to a linear function may not be representative of current use). The resubmission did not adequately justify the drop-off definition used to estimate patient numbers. The inclusion of children was not consistent with the proposed restriction for tirzepatide. DUSC agreed with the evaluation.
Metformin switch outs who have an SGLT2 inhibitor contraindication	3.1%. Cross-sectional study of CKD prevalence in US adults with type 2 diabetes based on the National Health and Nutrition Examination survey datasets from 2007-2012 (Wu 2016). The resubmission assumed that the sum of age-adjusted prevalence of CKD Stage 4 (eGFR 15-29) and CKD Stage 5 (eGFR <15) would be representative of the	CKD prevalence estimates in the US setting may not be applicable to the Australian setting due to differences in population characteristics. DUSC agreed with the evaluation. DUSC considered this parameter to be underestimated and noted it is estimated 7.8% of the Australian type 2 diabetes population were classified with Stage 4 and 5 CKD.[6]

[6] Australian National Diabetes Audit. (2023). Australian National Diabetes Audit annual report 2022. Monash University, School of Public Health and Preventive Medicine. https://www.monash.edu/__data/assets/pdf_file/0003/3218205/anda-2022-final-annual-report.pdf

Data	Value applied and source	Comment
	proportion of patients with eGFR <30 (2.4% + 0.7%).	
Uptake rate in prevalent populations	Year 1: [redacted]%, Year 2: [redacted]%, Year 3: [redacted]%. A cumulative uptake of [redacted]% over 3 years was assumed, based on expert advice from Australian general practitioners, nurse practitioners and endocrinologists, which indicated that [redacted]% of prescribers would use GLP-1/GIP therapies in 80-100% of patients and [redacted]% of prescribers would use GLP-1/GIP therapies [redacted]-[redacted]% of patients who had previously trialled an SGLT2 inhibitor. The resubmission noted that the cumulative uptake was lower in the current resubmission compared to the November 2024 submission ([redacted]%).	The uptake rates estimated in the expert advice have no relevance to the uptake of tirzepatide in patients who are already using a GLP-1 therapy or have switched to other available therapies. DUSC agreed with the evaluation and noted the survey was based on patients who have never been treated with a GLP-1. DUSC noted the high awareness of semaglutide and considered it unlikely that [redacted]% of the prevalent population would switch to treatment with tirzepatide, particularly if patients have been stabilised on treatment. DUSC commented that the treatment uptake rate could be similar to what is observed in the SGLT2 market. The pre-PBAC response reduced prevalent pool uptake assumptions to a cumulative uptake of [redacted]% over 3 years.
Uptake rate in incident populations	Increasing from [redacted]% in Year 1 to [redacted]% in Year 3 onwards. Assumption based on expert advice from Australian general practitioners, nurse practitioners and endocrinologists which indicated that [redacted]% of prescribers would use GLP-1/GIP therapies in [redacted]-[redacted]% of patients and [redacted]% of prescribers would use GLP-1/GIP therapies in [redacted]-[redacted]% of patients who had previously trialled an SGLT2 inhibitor. The resubmission noted that uptake rates were lower in the current resubmission compared to the November 2024 submission ([redacted]% in Year 1 increasing to [redacted]% in Year 3 onwards).	The estimated uptake rates appear optimistic given the range of values estimated in the expert advice. DUSC commented on the uncertainty of the treatment uptake estimates given the revised values in the resubmission followed an upward trend, compared to the downward trend applied in the November 2024 submission ([redacted]% to [redacted]%). The pre-PBAC response reduced the incident population uptake assumptions to [redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Year 3, [redacted]% in Year 4, [redacted]% in Year 5 and [redacted]% in Year 6.
Treatment persistence (all therapies)	2nd year: 92.6%, 3rd year: 94.8%, 4th year: 90.0%, 5th year: 81.4%, 6th year: 70.6% Estimates derived from the cost-effectiveness model based on the assumption that patients only discontinue GLP-1/GIP therapy due to initiation of insulin or death. The resubmission noted that treatment persistence rates were generally lower in the current resubmission compared to the November 2024 submission (91.02% in all subsequent years)	In clinical practice, patients are likely to discontinue treatment for a variety of reasons other than initiation of insulin or death. International estimates on tirzepatide utilisation suggest that 73.3% of patients were persistent with therapy after 6 months (<45-day gap between prescription refills; Mody 2025). The treatment persistence estimates were based on patients stopping GLP-1/GIP therapy in order to initiate insulin and therefore cannot be used to inform utilisation estimates of tirzepatide in combination with insulin. The resubmission assumed that all therapies (tirzepatide, semaglutide, dulaglutide and DPP4 inhibitors) would have identical patterns of treatment persistence. This assumption was implausible given the differences in mode/frequency of administration as well as efficacy and safety profiles. This assumption was also inconsistent with the base case economic analysis which assumed that patients would be able to remain on tirzepatide therapy for longer than semaglutide

Data	Value applied and source	Comment
		which would therefore lead to market expansion. This assumption was also inconsistent with the clinical data which suggested higher rates of treatment discontinuation in patients using the higher tirzepatide dose strengths. DUSC noted that persistence was not relevant to a prevalent uptake approach. DUSC agreed with the evaluation that in clinical practice, patients are likely to discontinue treatment for a variety of reasons other than initiation of insulin or death. The PSCR argued that persistence rates reported by Mody 2025 do not reflect clinical practice and noted that Mody 2025, "highlighted that supply shortages could have impacted the dosing, and escalation and de-escalation." However, DUSC noted other observational studies have demonstrated similar findings to Mody 2025.[7,8] DUSC agreed with the commentary that it was implausible to assume all therapies would have identical patterns of treatment.
Treatment utilisation		
Scripts per patient per year (all therapies)	12.09. Calculated based on a tirzepatide script duration of 28 days and assumed treatment adherence of 93%. The resubmission claimed that lower adherence would be expected in clinical practice compared to the observed estimates from the SURPASS-2 trial (95%). The resubmission noted that adherence was lower in the current resubmission compared to the November 2024 submission (100%).	The assumption of 93% adherence is unlikely to reflect clinical practice. International estimates on tirzepatide utilisation suggest that only 57.5% of patients were highly adherent to therapy (proportion of days covered >80%; Mody 2025). The resubmission used the same adherence rate for all therapies (tirzepatide, semaglutide/dulaglutide, DPP4 inhibitors) which was implausible given the differences in mode/frequency of administration as well as efficacy and safety profiles. DUSC noted based on PBS data, approximately 6.8 semaglutide prescriptions were supplied per patient and 5 dulaglutide prescriptions were supplied per patient in 2023, noting these numbers encompass initiations and discontinuations in the year. DUSC agreed with the evaluation and noted similar findings in other observational studies[7,8] and considered the adherence estimate to be overestimated. The pre-PBAC response reduced assumed adherence from 93% to 83%. The pre-PBAC response stated that this was

[7] Buckley, A., Suliman, S., Allum, M., & others. (2024). Real world use of tirzepatide in the treatment of type 2 diabetes in an Arab population. Diabetes, Obesity and Metabolism, 26(8), 3381–3391. https://doi.org/10.1111/dom.15680

[8] Kelly, M. S., Scopelliti, E. M., Goodson, K. E., Lo, C. M. A., Nguyen, H. X., & Simon, B. (2024). Real-world evaluation of the effects of tirzepatide in patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism, 26(12), 5661–5668. https://doi.org/10.1111/dom.15934

Data	Value applied and source	Comment
		reasonable based on the efficacy of tirzepatide and the option to escalate the dose of the drug to achieve treatment goals. The pre-PBAC response argued that the mean semaglutide prescriptions in 2023 (6.8) were unreliable due to supply constraints and due to not all patients receiving treatment for the entire year.
Tirzepatide dose distribution	5 mg: [redacted]%, 10 mg: [redacted]%, 15 mg: [redacted]%. Based on a sponsor-commissioned survey of Australian general practitioners (5 mg: [redacted]%; 10 mg: [redacted]%; 15 mg: [redacted]%) and endocrinologists (5 mg: [redacted]%; 10 mg: [redacted]%; 15 mg: [redacted]%) on the likely tirzepatide maintenance doses used in clinical practice. Estimates were weighted assuming that 80% of tirzepatide scripts would be written by general practitioners. The dose distribution in the November 2024 submission was based on estimates from endocrinologists only.	This estimate appeared reasonable for the base case although the likely distribution of tirzepatide doses in clinical practice is highly uncertain. The PSCR noted Mody (2025) considered that supply shortages could have impacted the dosing, and escalation and de-escalation. DUSC noted other observational studies showed lower doses in clinical practice compared to the submission's estimates.[7,8] DUSC considered the dose distribution should be revised to: • 5 mg: 35% • 10 mg: 43% • 15 mg: 22%. The pre-PBAC response accepted the dose distribution proportions proposed by DUSC.
Tirzepatide cost per script	5 mg: $[redacted], 10 mg: $[redacted], 15 mg: $[redacted] The resubmission noted that proposed effective prices were lower in the current resubmission compared to the November 2024 submission (5 mg: $[redacted]; 10 mg: $[redacted]8; 15 mg: $[redacted]).	The estimated costs for tirzepatide were based on 30-day dispensing. However, the resubmission also requested consideration of 60-day dispensing for tirzepatide. No analyses were presented to assess the impact of 60-day dispensing.

Source: 'A7.1_Tirzepatide Section 4 Model (revised)' Excel workbook provided during the evaluation.
Abbreviations: DPP4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.
The redacted values correspond to the following ranges:
[1] *300,000 to < 400,000*
[2] *40,000 to < 50,000*
[3] *80,000 to < 90,000*
[4] *100,000 to < 200,000*
[5] *90,000 to < 100,000*

6.79 The estimated utilisation and financial implications of listing tirzepatide on the PBS/RPBS for the treatment of type 2 diabetes is summarised in Table 18.

Table 18: Estimated use and financial implications

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Total treated patients						
Resubmission	[redacted] 1	[redacted] 2	[redacted] 3	[redacted] 4	[redacted] 5	[redacted] 5
pre-PBAC response no changes to uptake rates [a]	[redacted] 1	[redacted] 2	[redacted] 3	[redacted] 4	[redacted] 5	[redacted] 5
pre-PBAC response plus changes to uptake rates [b]	[redacted] 6	[redacted] 1	[redacted] 2	[redacted] 3	[redacted] 3	[redacted] 4
Total tirzepatide scripts						
Resubmission	[redacted] 7	[redacted] 8	[redacted] 9	[redacted] 10	[redacted] 11	[redacted] 11
pre-PBAC response no changes to uptake rates [a]	[redacted] 7	[redacted] 8	[redacted] 9	[redacted] 10	[redacted] 10	[redacted] 10
pre-PBAC response plus changes to uptake rates [b]	[redacted] 12	[redacted] 13	[redacted] 8	[redacted] 8	[redacted] 9	[redacted] 9
Total tirzepatide costs (effective DPMQ less copayment)						
Resubmission	$[redacted] 14	$[redacted] 15	$[redacted] 16	$[redacted] 17	$[redacted] 18	$[redacted] 18
pre-PBAC response no changes to uptake rates [a]	$[redacted] 14	$[redacted] 19	$[redacted] 15	$[redacted] 16	$[redacted] 17	$[redacted] 17
pre-PBAC response plus changes to uptake rates [b]	$[redacted] 20	$[redacted] 21	$[redacted] 19	$[redacted] 15	$[redacted] 15	$[redacted] 16
Cost offsets for substituted therapies less copay						
Resubmission	-$[redacted] 20	-$[redacted] 14	-$[redacted] 21	-$[redacted] 19	-$[redacted] 19	-$[redacted] 15
pre-PBAC response no changes to uptake rates [a]	-$[redacted] 20	-$[redacted] 14	-$[redacted] 21	-$[redacted] 19	-$[redacted] 19	-$[redacted] 15
pre-PBAC response plus changes to uptake rates [b]	-$[redacted] 22	-$[redacted] 20	-$[redacted] 14	-$[redacted] 21	-$[redacted] 21	-$[redacted] 21
Net PBS/RPBS cost						
Resubmission	**$[redacted] 22**	**$[redacted] 20**	**$[redacted] 14**	**$[redacted] 14**	**$[redacted] 14**	**$[redacted] 14**
pre-PBAC response no changes to uptake rates [a]	**$[redacted] 22**	**$[redacted] 22**	**$[redacted] 20**	**$[redacted] 20**	**$[redacted] 20**	**$[redacted] 20**
pre-PBAC response plus changes to uptake rates [b]	**$[redacted] 23**	**$[redacted] 22**	**$[redacted] 22**	**$[redacted] 22**	**$[redacted] 20**	**$[redacted] 20**

Source: 'A7.1_Tirzepatide Section 4 Model (revised)' Excel workbook provided during the evaluation.

Abbreviations: DPMQ, dispensed price for maximum quantity; GLP-1, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.

[a] Source: 'A7.1_Tirzepatide Section 4 Model (revised 3)' Excel workbook provided with the pre-PBAC response with no changes to the uptake rates proposed by the resubmission.

[b] Source: 'A7.1_Tirzepatide Section 4 Model (revised 3)' Excel workbook provided with the pre-PBAC response with the following changes to the Epidemiology Spreadsheet: C16 and C25 changed from [redacted]% to [redacted]%; D38 changed from [redacted]% to [redacted]%; E38 changed from [redacted]% to [redacted]%; F38 changed from [redacted]% to [redacted]%; G38 changed from [redacted]% to [redacted]%; H38 changed from [redacted]% to [redacted]%; I 38 changed from [redacted]% to [redacted]%. *The redacted values correspond to the following ranges:*

[1] *200,000 to < 300,000*
[2] *300,000 to < 400,000*
[3] *400,000 to < 500,000*
[4] *500,000 to < 600,000*
[5] *600,000 to < 700,000*
[6] *100,000 to < 200,000*
[7] *2,000,000 to < 3,000,000*
[8] *4,000,000 to < 5,000,000*
[9] *5,000,000 to < 6,000,000*
[10] *6,000,000 to < 7,000,000*
[11] *7,000,000 to < 8,000,000*

[12] *1,000,000 to < 2,000,000*
[13] *3,000,000 to < 4,000,000*
[14] *$300 million to < $400 million*
[15] *$600 million to < $700 million*
[16] *$700 million to < $800 million*
[17] *$800 million to < $900 million*
[18] *$900 million to < $1 billion*
[19] *$500 million to < $600 million*
[20] *$200 million to < $300 million*
[21] *$400 million to < $500 million*
[22] *$100 million to < $200 million*
[23] *$80 million to < $90 million*

6.80 The net cost to the PBS/RPBS was $100 million to < $200 million in Year 1, increasing to $300 million to < $400 million in Year 6, with a cumulative net cost of > $1 billion over the first 6 years of listing.

6.81 The estimated net cost to the PBS/RPBS in the current resubmission was substantially lower than in the November 2024 submission (cumulative net cost over 6 years: > $1 billion) and higher than estimates in the original July 2023 submission (cumulative net cost over 6 years: > $1 billion). This was despite the current resubmission having a substantially larger eligible patient population compared to either of the previous submissions. The reduction in cost relative to the size of the patient population was primarily due to lower proposed effective prices for tirzepatide, a different distribution of tirzepatide doses (with more use of lower dose strengths) and reduced treatment persistence.

6.82 The evaluation considered the budget impact estimates were highly uncertain due to inappropriate restriction of the prevalent population to patients using a GLP-1 analogue or SGLT2 inhibitor in 2024, reliance on historical data, inadequately justified uptake rates, implausibly high adherence rates, persistence rates that exclude combination with insulin as well as the assumption of identical adherence and persistence patterns for all therapies (tirzepatide, semaglutide, dulaglutide and DPP4 inhibitors).

6.83 The results of the sensitivity analyses indicated that the budget impact estimates were sensitive to the parameterisation of the 10% PBS sample analysis (e.g. treatment window, inclusion of patients classified as drop-offs), uptake rates, adherence rates and persistence rates, with the total cost of tirzepatide ranging from > $1 billion to > $1 billion over 6 years and the net cost (including substitutions) ranging from > $1 billion to > $1 billion over 6 years. None of these estimates were adequately supported in the resubmission.

6.84 DUSC considered the estimates presented in the resubmission to be high. The main issues were:

- DUSC commented that the extrapolations applied in the submission would not reflect future clinical practice and considered the estimates should be revised and extrapolated based on data following amendments to the restriction in June 2024.

- DUSC noted a greater number of patients were supplied 5 mg and 10 mg doses in clinical practice compared to the SURPASS trial and considered the dose distribution of tirzepatide in the estimates should be revised to: 5 mg 35%; 10mg 43%; and 15 mg 22%. The pre-PBAC response accepted the dose distribution proportions proposed by DUSC.
- The treatment uptake rates of up to [redacted]% in the prevalent population in the first three years of listing were overestimated as patients are unlikely to switch to tirzepatide if they have been stabilised on treatment. The pre-PBAC response revised uptake rate assumptions for both the prevalent and incident patient populations (see Table 17).
- The adherence estimates presented in the resubmission (93%, 12.09 prescriptions per patient) appear high for a type 2 diabetes treatment in clinical practice. The pre-PBAC response reduced assumed adherence from 93% to 83% (see Table 17).

6.85 The pre-PBAC response provided a revised Section 4 model which incorporated the dose distribution proportions advised by DUSC and assumed 83% adherence. Changes to uptake rates were included as an option in the revised Section 4 model provided with the pre-PBAC response. With changes to the dose distribution proportions and assumed adherence only, the net cost to the PBS/RPBS was $100 million to < $200 million in Year One increasing to $200 million to < $300 million in Year 6, with a cumulative net cost of > $1 billion over 6 years. Incorporating the uptake rates proposed by the pre-PBAC response (see Table 17) in the revised Section 4 model, the net cost to the PBS/RPBS was $80 million to < $90 million in Year 1 increasing to $200 million to < $300 million in Year 6, with a cumulative net cost of $900 million to < $1 billion over 6 years.

Quality Use of Medicines

6.86 The resubmission did not identify any quality use of medicines issues.

6.87 DUSC considered support should be provided for prescribers and patients to ensure adherence and the maximum effective dose is reached (such as through management of adverse events and specialist support) given the gradual and low titration in clinical practice.

Financial Management – Risk Sharing Arrangements

6.88 The resubmission proposed a risk sharing arrangement consisting of subsidisation caps in each of the first 6 years of listing, with government expenditure beyond these thresholds rebated to [redacted].

6.89 The sponsor acknowledged that, based on the expected utilisation of tirzepatide in the financial estimates, [redacted], the sponsor also provided [redacted].

6.90 Proposed subsidisation caps and [redacted] are summarised in Table 19.

Table 19: Proposed risk sharing arrangement

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Cost for tirzepatide 5 mg (effective DPMQ less copay)	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Cost for tirzepatide 10 mg (effective DPMQ less copay)	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Cost for tirzepatide 15 mg (effective DPMQ less copay)	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Total cost of tirzepatide	$[redacted][3]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][7]
Subsidisation caps	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
[redacted]	$[redacted]	$[redacted]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][2]
[redacted] ([redacted]%[a])	$[redacted]	$[redacted]	-$[redacted][8]	-$[redacted][9]	-$[redacted][10]	-$[redacted][10]
[redacted]	**$[redacted][3]**	**$[redacted][4]**	**$[redacted][5]**	**$[redacted][6]**	**$[redacted][6]**	**$[redacted][6]**

Source: 'A7.1_Tirzepatide Section 4 Model (revised)' Excel workbook provided during the evaluation.
Abbreviations: DPMQ, dispensed price for maximum quantity; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; RSA, risk sharing arrangement.
[a] [redacted].
The redacted values correspond to the following ranges:
[1] *$100 million to < $200 million*
[2] *$200 million to < $300 million*
[3] *$300 million to < $400 million*
[4] *$600 million to < $700 million*
[5] *$700 million to < $800 million*
[6] *$800 million to < $900 million*
[7] *$900 million to < $1 billion*
[8] *$40 million to < $50 million*
[9] *$70 million to < $80 million*
[10] *$90 million to < $100 million*

6.91 The evaluation considered the nominated subsidisation cap thresholds were not adequately justified. The evaluation considered the financial estimates were also highly uncertain, and it is unclear whether the nominated subsidisation thresholds would manage the cost of tirzepatide versus that for existing GLP-1 analogues when used in a broad patient population.

6.92 As outlined in paragraph 6.69, the pre-PBAC response suggested a risk sharing arrangement [redacted]. The pre-PBAC response stated that any risk sharing arrangement would need to include: (i) [redacted] (ii) [redacted] (iii) only rebate over-cap Commonwealth Expenditure [redacted] (iv) [redacted] The PBAC noted Department advice that the [redacted].

6.93 The pre-PBAC response proposed a risk sharing arrangement with expenditure caps based on [redacted], with over-cap Commonwealth Expenditure rebates [redacted] (Table 20). However, as outlined in Table 21, [redacted] The cost offsets for substituted therapy were also determined based on the dose distribution proportions advised by DUSC and an assumption of 83% adherence only. The pre-PBAC response stated that the proposal would result in a net cost to the PBS/RPBS of > $1 billion over the first 6 years of listing [redacted]

Table 20: Risk Sharing Agreement proposal

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Subsidisation caps based on Pre-PBAC response plus change to uptake rates					

Source: Table 3 of the pre-PBAC response with figures updated to match those determined using 'A7.1_Tirzepatide Section 4 Model (revised 3)' Excel workbook provided with the pre-PBAC response and with the following changes to the Epidemiology Spreadsheet: C16 and C25 changed from % to %; D38 changed from % to %; E38 changed from % to %; F38 changed from % to %; G38 changed from % to %; H38 changed from % to %; I 38 changed from % to %.

Table 21: Pre-PBAC response proposed risk sharing arrangement

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)
Pre-PBAC response no change to uptake rates	$	$	$	$	$	$
[$] (%[a])	$	$	$ [b] [9]	$ [b] [9]	$ [b] [9]	$ [b] [9]
Net Comm Exp	$ [1]	$ [2]	$ [3]	$ [4]	$ [4]	$ [5]
Cost offsets – pre-PBAC response no change to uptake rates	-$ [6]	-$ [1]	-$ [7]	-$ [2]	-$ [2]	-$ [3]
Net cost to R/PBS	$ [8]	$ [8]	$ [8]	$ [8]	$ [6]	$ [6]

Source: Table 4 pre-PBAC response, Attachment A7.1_Tirzepatide Section 4 Model (revised 3) – tabs 3c. Impact – prosed (eff), 'RSA proposal'.

a

[b] Figures updated to match those determined using 'A7.1_Tirzepatide Section 4 Model (revised 3)' Excel workbook provided with the pre-PBAC response and with the following changes to the Epidemiology Spreadsheet: C16 and C25 changed from % to %; D38 changed from % to %; E38 changed from % to %; F38 changed from % to %; G38 changed from % to %; H38 changed from % to %; I 38 changed from % to . Hence, the following changes to the RSA proposal spreadsheet: F80 = $; G80 = $; H80 = ; I80 = $.

The redacted values correspond to the following ranges:

[1] *$300 million to < $400 million*
[2] *$500 million to < $600 million*
[3] *$600 million to < $700 million*
[4] *$700 million to < $800 million*
[5] *$800 million to < $900 million*
[6] *$200 million to < $300 million*
[7] *$400 million to < $500 million*
[8] *$100 million to < $200 million*
[9] *$50 million to < $60 million*

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for tirzepatide for the treatment of adult patients with inadequately controlled type 2 diabetes mellitus to allow further consultation with the sponsor regarding achieving a cost-effective listing. In deciding to defer making a recommendation, the PBAC considered that tirzepatide was not cost-effective at the prices proposed in the resubmission. The PBAC reaffirmed its July 2023 advice that an incremental cost effectiveness ratio in the order of $30,000 per QALY would be appropriate. The PBAC was also concerned that if listed on the PBS, there was high likelihood that tirzepatide would be used for purposes other than for the treatment of type 2 diabetes mellitus. The PBAC considered that the risk sharing arrangements proposed would not adequately manage this risk to the Commonwealth.

7.2 The PBAC noted the input from individuals, health care professionals and organisations which, consistent with both the July 2023 and November 2024 submission consumer comments, highlighted the benefits of treatment with tirzepatide including a significant reduction in glycated haemoglobin (HbA1c) and weight loss. The PBAC noted the input highlighted the high cost of tirzepatide in the private market as a barrier to access. The Committee also acknowledged the comments from both the National Aboriginal Community Controlled Health Organisation (NACCHO) and the Diabetes Alliance which emphasised the disease burden experienced by Aboriginal and Torres Strait Islander peoples. Finally, the PBAC noted that a large proportion of the input from individuals was focused on a PBS listing for weight loss rather than type 2 diabetes mellitus, which supported the PBAC's view that the risk of use outside of the proposed indication was high.

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

- The change in the proposed target population from being restricted to a high-risk population (as per the November 2024 submission) to a broader population aligned with the current PBS restrictions for Glucagon-like Peptide 1 Receptor Agonists (GLP-1 analogues) was appropriate. The PBAC noted the broader population included all patients who are contraindicated, intolerant or inadequately controlled with a sodium glucose transporter-2 (SGLT2) inhibitor.
- An Authority required (telephone/electronic) listing for the initial treatment phase and an Authority required (Streamlined) listing for the continuing treatment phase was reasonable.
- One repeat for both initial and continuing treatment listings of the 2.5 mg, 7.5 mg and 12.5 mg tirzepatide doses was appropriate, as was five repeats for both initial and continuing treatment listings of the 5 mg, 10 mg and 15 mg tirzepatide doses.
- Use in combination with insulin should be allowed.

- The population criteria restricting use to patients at least 18 years of age be removed. The PBAC noted that removal would be consistent with the current PBS restrictions for GLP-1 analogues. .
- A grandfathering restriction which would allow use in patients who are contraindicated, intolerant or inadequately controlled with a SGLT2 inhibitor was reasonable.

7.4 The PBAC considered that the nomination of semaglutide as the main comparator was appropriate.

7.5 The PBAC noted that, as per the July 2023 and November 2024 submissions, the SURPASS-2 trial was the key clinical trial for the resubmission. With no change in this evidence the PBAC reaffirmed its previous advice that the claim that tirzepatide 10 mg once weekly and tirzepatide 15 mg once weekly were superior in terms of efficacy compared to semaglutide 1 mg once weekly in patients using metformin background therapy was reasonable (see paragraph 6.38). The PBAC also reaffirmed its previous advice that available data did not support superior efficacy of tirzepatide 5 mg once weekly versus semaglutide 1 mg once weekly (see paragraph 6.37). The PBAC acknowledged ESC advice that prescribing data indicated that tirzepatide 5 mg was widely used (see paragraph 4.6) and that the market research presented in the resubmission was not consistent with the claim that tirzepatide 5 mg should be considered a titration dose (see paragraph 5.3). The PBAC reaffirmed its previous advice that the comparison of tirzepatide 5 mg once weekly and semaglutide 1 mg once weekly was important (see paragraph 5.4). However, the PBAC considered that, with the removal of cost as a barrier to access, the proportion of patients assumed to de-escalate to or remain at tirzepatide 5 mg as a maintenance dose in clinical practice was less clear. As such, the PBAC considered it was reasonable to allow a small proportion of use of tirzepatide 5 mg once weekly to be considered a titration dose for which a comparison with semaglutide 0.5 mg once weekly would be appropriate. The PBAC reaffirmed its previous advice that the claim that tirzepatide 5 mg once weekly was superior in terms of efficacy compared to semaglutide 0.5 mg once weekly was reasonable.

7.6 The PBAC noted that the resubmission also presented a supportive comparison of tirzepatide 5 mg, 10 mg and 15 mg once weekly versus placebo in patients on background insulin glargine therapy (SURPASS-5). The PBAC noted that treatment with tirzepatide was associated with statistically significant reductions in HbA1c and in body weight from baseline to Week 40 compared to placebo in patients enrolled in the SURPASS-5 trial. The Committee acknowledged that the resubmission did not present comparisons of tirzepatide versus semaglutide when used in combination with insulin. However, the PBAC considered that the based on the evidence presented in the SURPASS-2 and SURPASS-5 trials it was reasonable to allow use of tirzepatide in combination with insulin, consistent with the current PBS listings of GLP-1 analogues. The PBAC considered that tirzepatide in combination with insulin would account for a minority of tirzepatide use (see paragraph 4.6).

7.7 The PBAC reaffirmed its July 2023 advice that the claim of non-inferior safety was not adequately supported by the data for any of the comparisons.

7.8 The PBAC noted the resubmission presented a modelled economic evaluation of tirzepatide 10 mg and 15 mg once weekly compared to semaglutide 1 mg once weekly and a scenario analysis comparing tirzepatide 5 mg once weekly with semaglutide 0.5 mg once weekly in patients using metformin background therapy. The resubmission also presented a sensitivity analysis that assumed that patients may remain on GLP-1/glucose-dependent insulinotropic polypeptide (GIP) therapy after insulin intensification. The PBAC noted that, consistent with the Committee's previous advice, the resubmission economic model increased the insulin intensification threshold (from HbA1c >7% to >8%). The PBAC also noted the resubmission economic model incorporated a reduction in the proposed effective price of tirzepatide (see paragraph 3.2). The PBAC noted the resubmission economic model did not address its previous recommendation for the economic model to incorporate biomarker drift for all variables or previous ESC advice that incorporation of the SURPASS-2 trial utility values while on first-line therapy would be informative. In addition, the PBAC noted that the hypoglycaemia rates with insulin in the economic model were substantially overestimated compared to observed estimates from the SURPASS clinical trial program. The PBAC agreed with the ESC that inclusion of UKPDS drift for all biomarkers, hypoglycaemia rates from SURPASS-4 with higher disutility per event and SURPASS-2 utility values while on first-line therapy were appropriate. The PBAC noted that Table 14 provided the incremental cost effectiveness ratios for the comparisons of tirzepatide 5 mg, 10 mg and 15 mg with semaglutide 1 mg for these revised inputs assuming tirzepatide/semaglutide treatment continuation after insulin initiation was allowed (Scenario 4) and not allowed (Scenario 5). Noting the similarity in the incremental cost effectiveness ratios reported for Scenario 4 and Scenario 5 and acknowledging that a minority of tirzepatide use is in combination with insulin, the PBAC advised that Scenario 5 in Table 14 should be used to determine the cost-effectiveness of tirzepatide.

7.9 The PBAC reaffirmed its July 2023 advice that an incremental cost effectiveness ratio in the order of $30,000 per QALY would be appropriate. The PBAC acknowledged that Scenario 5 with an incremental cost effectiveness ratio in the order of $30,000 per QALY incorporates a premium for tirzepatide 5 mg weekly over semaglutide 1 mg weekly that is not supported by the clinical data. Noting a proportion of tirzepatide 5 mg is likely to be a titration dose, and superiority has been established over semaglutide 0.5 mg weekly, the PBAC considered a small premium for tirzepatide 5 mg weekly over semaglutide 1 mg weekly to be reasonable. The PBAC considered the premium should be applied to the proportion assumed to be a titration dose and should be no larger than calculated using the economic model for the tirzepatide 5 mg versus semaglutide 1 mg comparison (see Table 15).

7.10 The price reductions required to achieve an incremental cost effectiveness ratio of $30,000 per QALY gained for Scenario 5 are outlined in Table 15. The PBAC noted the

effective dispensed price for maximum quantity proposed in the resubmission for the 5 mg, 10 mg and 15 mg tirzepatide doses would need to reduce from $[redacted], $[redacted] and $[redacted] to $[redacted], $[redacted] and $[redacted] respectively to achieve an incremental cost effectiveness ratio of $30,000 per QALY for Scenario 5. The PBAC noted the pre-PBAC response (and confirmed in the Sponsor hearing) stated that the Sponsor would only list on the PBS at the prices requested in the resubmission.

7.11 The PBAC agreed with DUSC that the financial estimates provided in the resubmission were extremely high and uncertain. The PBAC considered the additional costs of > $1 billion over the first 6 years was disproportionate to the modest additional benefits that tirzepatide might deliver over semaglutide in the treatment of type 2 diabetes mellitus. The PBAC considered that revisions to the financial estimates provided in the resubmission were required to address the uncertainty. The PBAC also agreed with DUSC that the extrapolations applied in the resubmission may not reflect future clinical practice, given the changes to the GLP-1 analogue restrictions in June 2024. The PBAC noted that an additional year of data was available for patients taking GLP-1 analogues following changes to the restrictions for these agents. The PBAC considered that the extrapolations for the prevalent patient population treated with GLP-1 analogues should be revised based on the additional data available from June 2024 onwards. The PBAC noted the concerns raised by DUSC that the incident SGLT2 inhibitor switch out population were already captured as part of the prevalent patient population and advised that they should be removed from the financial estimates. The PBAC accepted DUSC advice that the dose distribution of tirzepatide in the financial estimates should be revised to: 5mg 35%; 10 mg 43%; and 15 mg 22%. The PBAC noted the pre-PBAC response proposed amendments to address concerns raised by DUSC regarding overestimation of the treatment uptake rates and higher levels of adherence assumed than would be likely in clinical practice. The PBAC accepted the pre-PBAC response revisions to uptake rate assumptions for both the incident and prevalent patient population (see Table 17). The PBAC also accepted the pre-PBAC response proposal to reduce the assumed level of adherence from 93% to 83%. The PBAC advised that once updated with these amendments, and with the price reductions required to achieve an incremental cost effectiveness ratio of $30,000 per QALY gained for Scenario 5, it would be reasonable to accept the financial estimates as the basis of a risk sharing arrangement.

7.12 The PBAC advised that there was a high likelihood that tirzepatide would be used for purposes other than for the treatment of type 2 diabetes mellitus and considered a risk sharing arrangement would be required to mitigate the financial impact to the Commonwealth associated with use outside the restriction. The PBAC advised that any such risk sharing arrangement would need to be based on the revised financial estimates outlined in paragraph 7.11.

7.13 The PBAC noted the pre-PBAC response proposed a risk sharing arrangement [redacted] (see paragraph 6.92). The PBAC considered this approach was inherently uncertain as it relied on a high level of confidence in the utilisation estimates. Nonetheless, given

the context of the risk sharing arrangement outlined in the pre-PBAC response, the PBAC advised that [redacted]. The PBAC considered that it may be reasonable for the rebate for use above the agreed caps [redacted] However, the PBAC advised that a mechanism may also be required to ensure that the risk to the Commonwealth of use beyond type 2 diabetes mellitus is addressed.

7.14 The PBAC advised that without an approach that both achieves an acceptable incremental cost effectiveness ratio and mitigates the substantial risk to the Commonwealth of use outside of the proposed indication, the Committee could not recommend tirzepatide for type 2 diabetes mellitus.

Outcome:
Deferred

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.